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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

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February 20, 2015
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

RAJKUMAR D. RAO, M.D.	Panel Chair
S. RAYMOND GOLISH, M.D., Ph.D.	Voting Member
JEREMY GILBERT, PH. D.	Voting Member
LYNDA YANG, M.D., Ph.D.	Temporary Voting Member
STEPHEN J. HAINES, M.D.	Temporary Voting Member
CARL GRAF, M.D.	Temporary Voting Member
STEPHEN LYMAN, Ph.D.	Temporary Voting Member
DIRK ALANDER, M.D.	Temporary Voting Member
JOHN CARRINO, M.D., M.P.H.	Temporary Voting Member
JOSEPH P. O'BRIEN, M.B.A.	Patient Representative
KATHY TRIER, Ph.D.	Industry Representative
MONICA HARMON, M.S.N., M.P.H.	Consumer Representative
S.J. ANDERSON, M.P.H., LCDR, USPHS	Designated Federal Officer

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

MARK MELKERSON, M.S.
Director, Division of Orthopedic Devices
Office of Device Evaluation

LESLIE WOOLDRIDGE
Press Contact

FDA PRESENTERS:

ZANE W. WYATT, Ph.D.
Biomedical Engineer
Posterior Spine Devices Branch
Division of Orthopedic Devices
Office of Device Evaluation

ELIZABETH ADEGBOYEGA-PANOX, M.D.
Medical Officer, Orthopedic Surgeon
Anterior Spine Devices Branch
Division of Orthopedic Devices
Office of Device Evaluation

PABLO E. BONANGELINO, Ph.D.
Mathematical Statistician
General and Surgical Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics

ANNA GHAMBARYAN, M.D., M.S., Ph.D.
Interdisciplinary Scientist
Epidemiologic Evaluation and Research Branch 2
Division of Epidemiology
Office of Surveillance and Biometrics

SPONSOR PRESENTERS:

EARL R. FENDER
President & CEO
VertiFlex, Inc.

PIERCE D. NUNLEY, M.D.
Study Investigator, Superion Trial
Associate Professor, LSUHSC
Director, Spine Institute of Louisiana

STEPHEN REITZLER
Vice President, Clinical & Regulatory Affairs
VertiFlex, Inc.

GLENN STIEGMAN, M.S.
Vice President, Clinical & Regulatory Affairs
Musculoskeletal Clinical Regulatory Advisers, LLC

SCOTT BLUMENTHAL, M.D.
Medical Director, VertiFlex, Inc.
Spine Surgeon, Texas Back Institute
Clinical Assistant Professor, Orthopedic Surgery
UT Southwestern Medical School

SPONSOR ADVISORS:

FRED H. GEISLER, M.D., Ph.D.
The Chicago Back Institute

LISA FERRARA, Ph.D.
Owner/President
OrthoKinetic Technologies, LLC

OPEN PUBLIC HEARING SPEAKERS:

CHRISTINA SILCOX, Ph.D.
Senior Fellow
National Center for Health Research

KATHRYN SIMPSON, Ph.D.
Manager, Clinical and Regulatory Affairs
Orthopedic Surgical Manufacturers Association

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M E E T I N G

(8:00 a.m.)

DR. RAO: I would like to call this meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee to order.

I am Dr. Raj Rao, Chair of this Panel. I am an orthopedic spine surgeon at the Medical College of Wisconsin, where I'm Professor and Vice Chair of the department.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application sponsored by Superion Interspinous Process Spacer device, VertiFlex, Incorporated.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, your affiliation. And we'll begin on this end of the table.

DR. TRIER: My name is Dr. Kathy Trier, and I am currently employed by Corin USA. I am the Industry Representative on this Panel. My background is primarily in research methods and statistics, with a focus in the industry on hip and knee joints.

MS. HARMON: Good morning. My name is Monica Harmon. I'm with the University of Pennsylvania School of Nursing. I am the Consumer Representative for this Panel. My background is in public health nursing, working specifically with vulnerable populations.

MR. O'BRIEN: Good morning. I'm Joe O'Brien. I'm President and CEO of the

National Scoliosis Foundation. I'm also a four-time spinal surgery patient, and I am a Patient Representative.

DR. YANG: Good morning. I'm Lynda Yang. I am a spine and peripheral nerve surgeon at the University of Michigan. I also serve as the current Chair for the Neurologic Devices Panel.

DR. LYMAN: Stephen Lyman, Hospital for Special Surgery. I am a clinical epidemiologist and Director of the Healthcare Research Institute.

DR. GRAF: Good morning. My name is Dr. Carl Graf. I am an orthopedic spine surgeon at the Illinois Spine Institute in Chicago.

LCDR ANDERSON: Good morning. My name is Lieutenant Commander Anderson. I'm representing the FDA and the United States Public Health Service.

DR. GILBERT: Good morning. I'm Jeremy Gilbert. I am a Professor of Biomedical and Chemical Engineering at Syracuse University, and Editor-in-Chief for the *Journal of Biomedical Materials Research Part B*. My expertise is in biomaterials.

DR. GOLISH: I'm Raymond Golish. I am a practicing spine surgeon and orthopedic surgeon. My Ph.D. is in engineering. I'm currently the Medical Director of Research and a spinal surgeon at Jupiter Medical Center in Palm Beach, Florida.

DR. HAINES: I'm Steve Haines. I'm the Chairman of Neurosurgery at the University of Minnesota.

DR. ALANDER: Dirk Alander. I am the Chief of Spine Surgery at St. Louis University and Professor of Orthopedic Spine.

DR. CARRINO: Good morning. My name is John Carrino. I'm the Vice Chairman of

Radiology and Imaging and Professor of Radiology at Weill Cornell Medical Center and the Hospital for Special Surgery, and my expertise is imaging.

MR. MELKERSON: I'm Mark Melkerson. I am the Director of the Division of Orthopedic Devices, and a background in biomedical engineering.

DR. RAO: Thank you, all.

Members of the audience, if you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Lieutenant Commander Anderson, the Designated Federal Officer for the Orthopaedic and Rehabilitation Devices Panel, will make some introductory remarks.

LCDR ANDERSON: The Food and Drug Administration is convening today's meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a

particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket application for the Superion Interspinous Spacer device sponsored by VertiFlex, Incorporated. This device is indicated for those patients with impaired physical function who experience relief in flexion with symptoms of leg/buttock/groin pain, numbness and/or cramping, with or without back pain. The Superion Interspinous Spacer may be implanted at one or two adjacent lumbar levels in patients in whom treatment is indicated at no more than two levels from L1 to L5.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Dr. Kathy Trier is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Corin USA.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a

personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any other financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during the meeting and will be included as a part of the official transcript.

Thank you.

I will now read the Appointment to Temporary Voting Status Statement.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Orthopaedic and Rehabilitation Devices Panel for the duration of this meeting on February 20th, 2015:

Dr. Lynda Yang, Dr. Graf, Dr. Lyman, Dr. Haines, Dr. Alander, Dr. Carrino.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This has been signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on February 12th, 2015.

Before I turn the meeting back to Dr. Rao, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting,

Incorporated, telephone number (410) 974-0947.

Information on purchasing videos of today's meeting can be found at the table outside the meeting room.

Handouts of today's presentations are available at the registration desk.

The press contact for today's meeting is Leslie Wooldridge.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you would like to present during today's Open Public Hearing session, please register with AnnMarie Williams at the registration table.

All written comments received have been included in the panelists' folders and have been reviewed. A copy of the statements received may be viewed at the registration table.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Rao.

DR. RAO: Thank you, Lieutenant Commander Anderson.

We will now proceed with the Sponsor's presentation. I would like the Sponsor to approach the podium.

I will remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will have 92 minutes to present. It is now 8:13. You may begin your presentation.

MR. FENDER: Thank you, and good morning. I'm Earl Fender, President and CEO of VertiFlex, Inc. VertiFlex is the developer of the Superion Interspinous spacer, and we are the Sponsor of today's subject PMA.

FDA has raised important questions for this Panel to consider, and I want you to know that our company takes this matter very seriously and will present a full spectrum of study data to help you reach conclusions with which to advise the Agency. We've assembled a very well-qualified team of presenters to help with this today, and each of them has significant experience in this particular PMA trial. They, along with other content experts, will be available to answer questions as we proceed through the day.

One note on this chart. John Hipp, who is a radiologist from the core lab Medical Metrics, was unable to attend due to a family emergency.

Lumbar stenosis is a significant and growing problem in the United States. This is a disease which causes immense pain and could be quite debilitating for those affected. With over a million new diagnoses in the United States every year, of a mostly older population, stenosis-related hospitalizations and costly invasive surgeries are rising dramatically, with lumbar spinal stenosis being the number one reason that patients over the age of 65 have spine surgery.

So our principal objective for today is pretty simple. It's to address and directly answer the questions posed to you by FDA. In substantiating our trial design, we will present that the composite primary endpoint used in this trial is indeed appropriate for a

device indicated to treat moderate lumbar stenosis. The correct control device in the trial was selected, the X-STOP IPD device. It was selected because the indications of X-STOP are the same as for the Superion device; the mechanism of action is the same. And at the outset of the trial, X-STOP was the only device available to treat moderate lumbar stenosis. It was also a device deemed appropriate by FDA.

Per the protocol, Superion achieved non-inferiority at the trial's primary endpoint of 24 months. But while the protocol's complex composite primary endpoint resulted in success of over 50% in both arms of the trial, all of the individual components of the primary endpoint resulted in an overall success rate of over 80% in both arms of the trial, and also making it comparable to other available treatments to treat lumbar stenosis, including direct decompression.

In addressing radiographic observations, we will confirm that it is appropriate to compare different types of observations relating to both radiographic and overall success. While radiographic observations in this trial mostly lacked quick clinical sequelae, we have identified the principal risk factors and the mitigation methods that could be employed in an attempt to reduce spinous process fractures post-commercialization.

And then, finally, we will demonstrate safety, effectiveness, and a positive risk-benefit profile of Superion, noting durability of effect out to 36 months, beyond the 24-month primary endpoint.

Our first speaker this morning is Dr. Pierce Nunley, who is a study investigator. Dr. Nunley is Director of the Spine Institute in Shreveport, Louisiana.

DR. NUNLEY: Good morning. My name is Pierce Nunley, and I am an associate

professor at LSU Health and also the Director of the Spine Institute of Louisiana. I would like to disclose that I am a study investigator, and I also am receiving consulting time and travel for doing these proceedings.

I'm going to present the background for mild spinal stenosis -- mild to moderate stenosis that we studied in this trial.

As Mr. Fender remarked, spinal stenosis is a disease that affects millions of Americans and is quite prevalent in our society. The pathological state is a combination of multiple anatomic and pathophysiological phenomena, but principally that of compression of the nerve roots due to degenerative changes in the spine, the disc bulging, facet hypertrophy, and ligamentum hypertrophy. That ultimately leads to compression of the nerve roots, which leads to the symptomatology of spinal stenosis.

The clinical diagnosis of moderate stenosis is the first one, as I said, that's made clinically. It's how does a patient present, particularly with persistent buttock and leg pain, pain that's worse with extension and relieved with flexion? And that's a principal part of this study. And one of the definitions of moderate stenosis is that the patients had to get relief with flexion. And then, of course, it's confirmed radiologically. We have to find stenosis on the radiographic films and see the areas of nerve root compression.

I think it's important to understand the continuum of this disease, and it's a progressive disease, as we know. And so when we go from mild to moderate to severe stenosis, traditionally we've looked at treatment options in this continuum, and the early treatment options for mild stenosis have been non-operative management, and that has proven to be quite successful.

As we go up in grades of stenosis and grades of severity of symptoms, we get into indications for operative treatment, and traditionally the first line of treatment has been laminectomy, decompression, going and opening up the canal and allowing room for the nerves. Now, in severe stenosis and instability and spondylolisthesis and other diagnoses, the addition of pedicle screws and fusions, plus or minus inter-body devices, have been used to treat those more severe cases.

Interestingly enough, the idea of indirect decompression was first brought to the Agency with the X-STOP device, and the concept behind that was to -- for the less severe cases of stenosis, rather than do a larger procedure that has more complications and morbidity associated with it, we could do a less invasive procedure to block extension and prevent the stenosis-related symptoms that patients get in neurogenic claudication. And subsequent to that, the Agency has also seen a subsequent PMA of coflex, which is kind of hybrid of those. It is an interspinous process device, but it does combine a microscopic decompression as part of that.

But the important thing as we go forward today is to understand, one, the treatment, the patient that we're treating, which is moderate stenosis, not severe stenosis, and that we're trying to intervene earlier, still within the realm of when we typically operate, but earlier in that cascade of disease.

Direct decompression has many potential benefits. Certainly, it directly decompresses the neural elements, and it's effective in severe stenosis. It also has a proven history of reasonable effectiveness. It's typically a fairly straightforward operation. In recent years it has been done less invasively than previously, but nevertheless, even in its

presentation today, it has many potential risks. Some of those are that it's more difficult in an older population that's maybe more friable and more at risk with longer surgical procedures and blood loss and comorbidities, and it also has adverse risks such as epidural fibrosis, dural tears, deep wound infections, destabilizing the spinal segment, and also nerve injury.

The X-STOP device was first viewed by the Agency as to be a less invasive procedure. And this device blocks extension, which is the most painful position for stenotic patients. It does mitigate the risk discussed with decompression previously, such as epidural fibrosis and nerve injury and also deep infections, and it is Level I clinical evidence that demonstrates safety and effectiveness versus the non-operative control that was in that study. But the key in this device that I believe -- in Superion is it doesn't really limit surgical options in the future. And we'll discuss more about that later.

There remains difficulty comparing treatment options, and there's a tradeoff between indirect and direct decompression. We'll show that there's a similar effectiveness profile for this patient profile with moderate stenosis. And the risk profile, further, is poorly documented in the literature. It does suggest a higher reoperation rate for the indirect decompression. However, there are higher complications rates and intervention rates with direct decompression. And there remains, unfortunately, a lack of Level I evidence for decompression outcomes that we all would like to have in order to better help our patients in the future.

Direct decompression also is used to treat a wider range of patients. It's used to treat not only moderate stenosis and sometimes mild stenosis in the appropriate patient,

but also severe stenosis. And it also is confounded by various factors and those being age, comorbidities, and other factors, the patient's health, and also spinal instability and deformity.

So, in summary, stenosis treatment is really dictated by severity, symptomatology, pathology of the disease. And when my patient comes in with a diagnosis of moderate stenosis and has failed conservative management and wants to know what other options might they have, I have a choice now of indirect and direct compression. And depending how the pain function presents, typically we look first at what's the severity of the disease, and if I see that the patient has severe stenosis and is not better with flexion and those type of things, direct decompression is a great surgery that has had proven effectiveness and safety.

But for the less severe cases and patients with moderate stenosis, as we've seen in the X-STOP trial and we'll see with the Superion data, a minimally invasive noninvasive canal procedure, such as these interspinous process devices, is a good clinical option for those patients.

I thank you for your attention at this point, and I would like to turn the podium over to Mr. Stephen Reitzler, who's the VP of clinical affairs for VertiFlex. Thank you.

MR. REITZLER: Thank you, Dr. Nunley.

I am, as stated, Steve Reitzler, Vice President of Clinical and Regulatory Affairs for VertiFlex. Thank you for the time today. I'd like to begin by presenting a brief description of the device, its implantation technique, its indications for use, and an overview of the clinical trial design.

Briefly, the Superion Interspinous Spacer is a one-piece implant available in five sizes, from 8 mm to 16 mm, in 2 mm increments. It's composed entirely of titanium alloy conforming to a recognized ASTM standard. ASTM recognizes this material as safe for implant use, and it's widely employed in numerous orthopedic and spinal implant applications. The device consists of an implant body to which are attached two rotating cam lobes or wings, as shown here.

The device has been subjected to substantial mechanical and biomechanical preclinical testing. It was engineered to be able to withstand expected spinal loads, and this has been demonstrated by the absence of any device breakage, collapse, or other structural failure in this clinical trial.

The implant is inserted through a cannula placed at midline in an undeployed or closed position with the two cam lobes parallel to the axis of the implant body. Through the use of a manual instrument, these cam lobes are rotated away from the implant body to the fully deployed or open position shown on the right, here. In this state, the implant is locked with the superior and inferior cam lobes capturing the lateral aspects of the spinous processes between which the device was placed.

These images depict the placement of the Superion spacer in situ in both A/P and lateral views. In this state, biomechanical studies have established that the device measurably restricts or blocks extension.

The Superion device is implanted in a minimally invasive or percutaneous procedure with device positioning visualized by imaging techniques. The procedure begins with a small 12 mm to 15 mm stab wound, and through sequential dilation, the longitudinal fibers

of the supraspinous ligament are separated, and a working cannula, roughly the diameter of a quarter, is inserted to access the space between the two spinous processes. At the surgeon's discretion a burr may be inserted to prepare the space between the processes and remove soft tissue.

A gauge is then inserted to establish the appropriate implant size, and the implant is placed on a manual inserter positioned between the spinous processes and opened to the fully locked position. Cannula and driver are then removed, leaving the implant in place. The small incision is then sutured closed, and at the discretion of the surgeon, the separated supraspinous ligament fibers may also be approximated. And this was done in roughly 40% of the Superion cases.

The indications for use for the Superion device are presented here, and essentially, the device is indicated for use in that subset of patients described by Dr. Nunley previously, notably, in patients suffering from symptoms of neurogenic intermittent claudication secondary to a diagnosis of moderate lumbar stenosis, where stenosis is confirmed radiographically and importantly in those who achieve a relief from symptoms in flexion.

In collaboration with FDA during the IDE approval phase, the PMA-approved X-STOP device was selected as the control device for a number of reasons, as mentioned earlier by Mr. Fender. They have virtually identical indications for use, have the same or similar mechanism of action by placement to the interspinous space, and they have a similar risk profile and predicted similar safety and effectiveness profiles.

The study was designed as a prospective, multicenter trial randomized against the PMA-approved X-STOP device. Randomization was 1:1, with randomization occurring after

consent and confirmation of eligibility. Patients were blinded to their treatment arm.

The statistical plan was a Bayesian non-inferiority design with a 10% non-inferiority margin. Twenty-eight non-randomized training patients were initially treated, and among the randomized population, 190 were treated with the Superion device and 201 patients with the control device.

As shown here, follow-up visits were conducted at discharge, at 6 weeks, and at 3, 6, 12, 18, and 24 months and has continued annually thereafter. A variety of subgroup analyses have been conducted, including those for demographics characteristics, operative metrics, and radiographic observations.

Eligibility criteria for the trial were designed to include the moderate stenosis patients described by Dr. Nunley, based upon both functional and radiographic criteria. Inclusion criteria were designed to exclude those whose condition was not yet severe enough to warrant a surgical intervention, and to include those exhibiting moderate functional impairment and, as I said earlier, relief from symptoms in flexion.

Exclusion criteria included those designed to eliminate from participation those whose condition was severe enough to warrant more significant surgical intervention, for instance, those with fixed motor deficit, unremitting pain in any position, those with degenerative scoliosis, significant instability of the lumbar spine, and/or spondylolisthesis greater than Grade 1.

The primary endpoint in this study was a complex composite endpoint which included effectiveness measures, safety measures, consideration of additional and potentially confounding treatments, and radiographic observations. To be deemed a study

success, a patient had to meet all of the following criteria at the 24-month endpoint:

Clinical outcomes were measured using the Zurich Claudication Questionnaire, or ZCQ, which is a patient self-reporting tool validated for evaluation of lumbar spinal stenosis and consisting of three sections or domains: a physical function domain, a symptom severity domain, and a patient satisfaction domain. Success was defined as achievement of a minimum clinically significant improvement over baseline in any two of the three ZCQ domains.

In addition to being a success in accordance with the ZCQ metric, to be considered a study success, a patient could not have had any reoperation, revision, device removal, or supplemental fixation at the treatment level.

In addition to being a ZCQ success and having no reops or revisions, a patient could not have had any confounding treatment that could mask or interfere with assessment of the study devices. Such treatments included epidural steroid injections or selected nerve root blocks at the index level, rhizotomies, or spinal cord stimulators.

And, finally, to be a study success, the patient must not have had any major implant- or procedure-related complications. These included radiographic observations such as device dislodgment, migration, or spinous process fracture, new or persistent worsened neurological deficit, deep infection, death, or other permanent device-related disability. Again, primary endpoint success required that a patient meet all of these criteria, setting an extremely high bar for primary endpoint success.

In addition to the primary endpoint, a number of secondary outcomes were also assessed, including the Oswestry Disability Index, which is principally a back pain and

function metric; both leg and back pain as measured using the Visual Analogue Scale; quality of life as measured by the SF-12 health survey; and a Sponsor-designed patient satisfaction questionnaire.

To assure consistency in interpretation of radiologic observations, all radiographic analyses were performed by an independent core lab, Medical Metrics, Incorporated, or MMI. MMI is highly qualified by training, expertise, and technological sophistication to conduct such assessments. And parenthetically, MMI was also the core lab employed in the coflex trial. Radiographic assessments included both quantitative and qualitative observations, as are listed here.

The MMI review was utilized to determine such radiographic observations as spinous process facture, device migration, and device dislodgment. To do so, MMI examined all neutral and flexion-extension radiographics from all follow-up visits. Sequential review of imaging enabled assessment to changes occurring over time. For example, to detect fractures in addition to observing evident lucencies, software was used to stabilize the vertebral body such that any change in position of the spinous process between successive films would be immediately apparent and suggestive of a facture and warrant closer examination.

This methodology has proved extremely sensitive for the detection of fractures, and so much so the Sponsor and MMI are confident that CT is not necessary to identify fractures when this technology is employed.

Further, device migration was defined as device movement of over 5 mm in the A/P plane, and device dislodgment was defined as a device whose superior or inferior wings

were no longer in contact with the spinous process, or a device that was completely extruded.

Patient cohorts included the intent-to-treat population, which consisted of all randomized patients who were consented, screened, and scheduled for surgery, and who had an anesthesia start time. Modified ITT population consisted of randomized subjects with an anesthesia start time recorded, but where a patient who received no device or the wrong device would be considered a study failure. And, finally, the per-protocol population. Notably, there was no difference in this study between the ITT and the mITT populations.

As indicated previously, this trial was based upon a Bayesian posterior design for assessing non-inferiority using a complex composite primary endpoint. Non-informative priors were employed in analyses. Follow-up for the study is complete with all 24-month data having been acquired by mid-December 2013 and all 36-month data by January of this year. Bayesian simulations in the study design phase established that a 0.958 threshold was sufficient to control for Type I error.

To summarize, then, the Superion clinical trial was conducted using an a priori design and protocol prospectively approved by FDA using a PMA-approved control device appropriate for the indicated patient population.

All radiographic assessments were performed by a highly qualified and independent core lab.

An independent clinical events committee adjudicated all adverse events determined by a clinical investigator to be either related or of unknown or undetermined

relationship to the device, the procedure, or to an adjacent level.

And, finally, follow-up and patient retention was excellent at over 94% overall at 24 months.

Thank you for your time. And I'd like to introduce Glenn Stiegman, who will walk us through the data.

MR. STIEGMAN: I am Glenn Stiegman, Vice President of Clinical and Regulatory Affairs for Musculoskeletal Clinical Regulatory Advisers. That's a consulting firm. They concentrate in musculoskeletal and spine technologies. I am a consultant to VertiFlex, and I get paid for my time and travel.

So Mr. Reitzler has described the study design, and I'm going to take the next 20, 25 minutes to describe a lot of the study results. To really understand and analyze a study lies with the amount of missing data and patient accountability. For this study, 470 patients were consented in a randomized -- after you remove the post-consent screen failures and the training patients, you get your ITT group, your randomized cohort of 391 patients. This represented 190 Superion patients and 201 X-STOP patients.

As Mr. Reitzler described, there was a modified intent-to-treat group where the lack of anesthesia time, and if the patient got no device, were considered failures. However, there were no patients that met that category, so the modified intent-to-treat group was exactly the same as the intent-to-treat group, again 190 Superion patients and 201 X-STOP patients. If you remove the protocol violators and the missing patients at 24 months, you get the per-protocol cohort of 351 patients. At 24 months, this study had greater than 94% follow-up in both arms.

So working our way through the results, we first look at the patient demographics so we understand the makeup of the patient population. VertiFlex analyzed all demographic categories. Today I'm only presenting a few of these categories. As you can see, there were no real differences in any demographic category. When you evaluate the continuous variables such as BMI and age, you see no statistical difference. If you were to analyze the demographic categorical variables such as gender or spondylolisthesis, again you see no difference.

We evaluated the type of stenosis enrolled in the study. Primarily, it was a mixed bag of central and lateral stenosis, with central stenosis and lateral stenosis alone.

And, finally, a summary of the intraoperative variables. You see an even split between the one-level and two-level patients.

When you evaluate the perioperative measurements, both procedures are minimally invasive, especially when compared to other spinal stenosis treatment options such as decompression. The blood loss for Superion was minimal. The hospital length of stay was just under 2 days, and the operative time was just under an hour. While these values have shown statistical significance given the relative values to more invasive surgeries, VertiFlex doesn't necessarily consider these differences to be clinically significant. Overall, it simply demonstrated that both these interspinous devices demonstrated little invasiveness and morbidity during surgery.

Turning our attention to the primary endpoint that Mr. Reitzler described, this is a very complex and thorough primary endpoint. It encompassed clinical outcomes that measured pain and function, safety outcomes focusing on reops and revisions, additional

treatments that could confound the data, and potential complications that really takes on, as you will see later, the benefits and risks of both technologies.

Evaluating pain and function. The Zurich Claudication Questionnaire is a validated measure for spinal stenosis. It is made up of three domains: symptom severity, physical function, and patient satisfaction. It has been validated that a clinically significant difference of 0.5 is the clinically significant difference. That is the green dotted line on this particular graph, where its position is based on the starting point of the patients.

Using this graph, as you can see, there is a clinically significant improvement by 6 weeks in both treatments. Not only do you see the improvement in clinical symptoms in the symptom severity category, you also see maintenance of that improvement through 24 months and into 36 months.

Assessing physical function. Again, 0.5 is a clinically significant difference, represented by the green dotted line. By 6 weeks you see that the patients have met their clinically significant improvement, and that is maintained through 24 months and into 36 months.

In both the symptom severity and the physical function, you see a tremendous effect of the device, keeping in mind that these patients have already exhausted over 6 months of unsuccessful non-operative care.

Lastly, if you look at patient satisfaction, the success criteria of patient satisfaction is less than or equal to 2.5. These patients demonstrated a high rate of satisfaction at the earliest possible time point, which is 6 weeks. So when you think about what Dr. Nunley stated earlier about the decision between indirect decompression and direct

decompression, this measurement is fairly compelling because these patients have shown a high level of satisfaction of the treatment they received.

Moving on to reoperations and revisions. Essentially, both of these devices had a similar safety profile. There was no significance difference in revision rates. Of those that had revisions, there was a similar rate of those patients that went on to decompression, with 13.7% in the Superion group and 11.4% in the X-STOP group. We did see, however, an increase in revisions in the X-STOP group between 24 and 36 months. Overall, at 24 months we saw a 20% revision rate compared to a 14.4 revision rate, which was not statistically significant, and that rate grew closer at the 36-month time point.

Where we take a closer look at the cause of reoperations and revisions, we subdivided the reoperations and revisions based on the underlying cause of that revision. As noted in this table, the majority of the reoperations were due to lack of initial efficacy, the return of symptoms, and disease progression in both treatment groups. Only a minor number of reoperations and revisions were due to safety-related reasons such as dural tear, infection, or fracture.

The endpoint regarding additional treatments consisted of those treatments that could confound the data, such as epidural injections, nerve root blocks, spinal cord stimulation, and rhizotomies. As you can see, the study demonstrated similar rates of epidurals, with X-STOP having a slightly higher number of injections for pain compared to Superion.

Lastly, evaluating the complications which primarily encompassed neurologic failures and radiographic observation. This endpoint is really about risk. What observations could

lead to a potential safety concern whether it's a transient neurologic deficit or a spinous process fracture? So the reason we are here today is to discuss these radiographic observations and what they mean.

First, the rate of radiographic observations in this study demonstrated an 11.1 rate for Superion and a 13.9 rate for X-STOP. Radiographic observations consisted of spinous process fractures, device migrations, and device dislodgments. Failure of these three categories were for spinous process fractures as non-healed at 24 months; for device migration, failure was defined as A/P migration of greater than 5 mm; and device dislodgment where the superior or inferior wings were no longer in contact with the bone and/or the device is completely extruded from the spine.

When you combine all of these components, note that each patient had to be a success in every category. So, in other words, a patient could be a ZCQ success at 24 months and had no revisions or reoperations, that had an epidural injection at 3 months -- that would be considered a failure. Therefore, when taking all of this into account, you get a success rate of 52.7 for the Superion group and 50.2 for the X-STOP group. This analysis was performed on all randomized patients, and based on the a priori determined posterior probability for non-inferiority, this difference allowed Superion to be deemed non-inferior. If you look at the per-protocol cohort, you see a slightly bigger difference. We are very confident in this result because the missing data is minimal because of the high follow-up rate. Therefore, the statistical robustness as needed to demonstrate a confident conclusion is present to show non-inferiority.

Now, the FDA has questioned the overall success rate, especially compared to that in

the literature. So VertiFlex wanted to present how each endpoint was actually a tremendous success for these patients and once combined equals the rate shown in the prior slide. So, by breaking out each endpoint, you see how well these patients did, and both groups reaching above 80% in each endpoint category. Compared to literature which we will see later, this is remarkable, especially if you compare the other options such as direct decompression or direct decompression and fusion.

So, overall, VertiFlex demonstrated clear clinically significant improvement when using Superion; demonstrated that patients that needed to get revised, it was due to lack of treatment effect or progression of the disease and not for safety reasons. We saw that the X-STOP had a slightly higher rate of epidural injections to manage the patient's pain. And, finally, we saw a similar complication, especially when considering the similar rates of radiographic observations.

Looking at the secondary outcomes, you will see the same trend over and over. First, looking at VAS worse leg pain. A clinically significant improvement in VAS is 20 mm. Again, this is where the green dotted line is located based on the patient's entry average. As you can see again, by 6 weeks the patient is clinically significantly improved, and that improvement is maintained through 24 months and then 36 months. This is another representation of the treatment effect of Superion.

In the realm of back pain, the same trend exists with Oswestry Disability Index and VAS back pain. Not all patients had back pain. This was not an entry criteria, but nonetheless you still see the same trend of improvement. With all of these measurements, after receiving the Superion, patients had improvement of their stenosis symptoms, their

back pain, and their leg pain.

Moving on to radiographic outcomes. The primary mechanism of action is to block the painful motion, which is extension, which we were able to see through 24 months. We saw no difference in flexion-extension angles between the Superion and X-STOP. We saw no difference in the amount of distraction at 24 months. However, we did see a greater amount of distraction as measured by foraminal height, lower disc angle, and higher posterior disc height in the X-STOP group, but by 24 months, both groups equaled the other.

If you look at the radiographic data combined with the clinical outcomes, we think there's a clear indication that the Superion is meeting its mechanism of action, which is blocking extension.

So VertiFlex has demonstrated non-inferiority when evaluating the composite endpoint compared to X-STOP, and if you look at each individual endpoint, they had a greater than 80% success rate. This is important because the FDA is again questioning the 52% success rate of the composite endpoint when that may not be a clear representation of how they're doing clinically. As we will demonstrate later, these rates are comparable to other studies in the literature cited by the FDA. Not only did patients have a high rate of success in each endpoint, all got better clinically, which can be attributed to the device actually doing what it's supposed to do, which is block extension. All in all, patients achieved a consistent, meaningful, and lasting clinical improvement.

Now turning our attention to safety, as with any IDE, all adverse events, regardless of the relation to the device or procedure, were reported by the study investigator. The

overall rates were similar between the Superion group and the X-STOP group. The relationship of the adverse events to the device or procedure were also reported by the investigator in categories of related, not related, unknown or undetermined, which could be considered maybe a "possibly" type category. The rates of device- or procedure-related adverse events were also similar between groups, with no device- or procedure-related deaths.

The FDA has also requested what we consider a worst-case analysis where we combine all of the unknown, undetermined, and definitely related events together. That assessment will be presented by the FDA.

The FDA has asked questions related to the incidence of spinous process fractures in this class of device, in particular, the difference between rates of fracture reported by the sites compared to that reported by the core laboratory, MMI. Adverse events of spinous process fractures were reported by each investigator. In the adverse events that were denoted by the investigator as definitely or possibly related to the device, the CEC, the clinical events committee, reviewed these events. Often the CEC would recategorize events to a fracture event based on the descriptions within the narrative, review of the x-rays, or possibly a review of the core laboratory report, which are the final numbers reported in all the safety tables within the PMA and presented here.

In contrast, the report of fractures from the independent core lab were based on a systematic review of all radiographics, separate from any clinical relation. This independent analysis was utilized for the primary endpoint to allow the standardization of this radiographic assessment. Patients with a spinous process fracture that has healed prior to

Month 24 were not considered failures for the composite endpoint.

In summary, the Superion provides a similar safety profile compared to X-STOP, which again justifies it as a valid control for the Superion. We saw similar rates of procedure-related AEs, a similar rate of device-related AEs, and the reop and revisions were similar in both arms.

Per the protocol, VertiFlex followed patients out annually after 24 months. As you can see, looking at the ZCQ scores, the symptom severity score again held constant between 24 and 36 months, therefore showing a continued long-term clinical effect out to 3 years.

For physical function, again you see the same exact trend where the device or the clinical improvement held constant between 24 and 36 months.

And, lastly, the patient satisfaction scores demonstrated the same trend as shown at the 24-month time point. At 36 months, 91.5% of the Superion patients met the minimally clinical improvement in patient satisfaction.

If we were to use the same composite endpoint as performed at 24 months, we saw a rate of 52.5% success for the Superion and 38% success for the X-STOP. There were no new spinous process fractures during this period, and the success rate is based on 90% of patients that were available at that time. Therefore, VertiFlex believes that Superion has shown long-term data that the device has a continued and stable treatment effect.

Quickly looking at the secondary endpoints at 3 years, we see that Superion showed a continued improvement out to 36 months, which again is a measurement that demonstrates the effect of the device. VAS back pain also demonstrated the same trend.

By evaluating all of these measurements, we see a continued and maintained improvement effect in the patients' pain for the Superion group.

So, to wrap up the study results, the Superion did demonstrate a reasonable assurance of safety and effectiveness, regardless of what the overall success rate was. The patients, as demonstrated, showed a significant clinical improvement in pain and function. Even out to 24 months and on to 36 months, this clinical improvement was intact. Given the amount of improvement, and if a patient were to be revised, it was primarily due to progression of the disease. And, overall, patients demonstrated a clear benefit when using Superion.

I'd now like to bring up Dr. Scott Blumenthal, who is going to discuss the radiographic observations from the Superion IDE.

DR. BLUMENTHAL: Thank you, Glenn.

My name is Scott Blumenthal. I am a spine surgeon at the Texas Back Institute. My disclosure is that I am a compensated co-medical director for VertiFlex.

The FDA has asked questions related to radiographic observations in the Superion clinical trial, specifically related to the incidence and clinical effect of spinous process fractures, device migrations, and device dislodgments.

This chart, which you have seen previously, shows that the -- as reported by Medical Metrics, that the overall rates of radiographic observations are comparable between the two groups, with the incidence of migration and dislodgments only seen in the X-STOP cohort.

Also in the X-STOP cohort, as shown in this Venn diagram, there is significant overlap

in the three observed types of radiographic observations, where in the Superion arm only fractures were seen and no migrations and dislodgments.

So, to investigate and analyze these radiographic observations, I'm going to present three different facets of analysis. First, I'm going to provide a characterization of the radiographic observations, then present the evaluation of how this affected our patients, the clinical outcomes. And, finally, we undertook to investigate the potential risk factors that could be mitigated and what we learned from the study, which could help with training of surgeons potentially in the future.

So looking at the time course of these radiographic observations, you can see that the majority of these fractures, migrations, and dislodgments occurred acutely in both arms with no additional observations after 12 months. And what this tells us is that this event is a perioperative or early postoperative phenomenon.

In terms of where these fractures occurred, the majority of the Superion fractures occurred coincident with the device, whereas the majority of the X-STOP fractures occurred anterior to the device. And I'll show it here a little bit more diagrammatically.

Finally, fracture healing was characterized as well, and this was as well done through the core lab, MMI, and it was found that 32.3% of Superion and 41.2% of the X-STOP fractures healed prior to the 24-month follow-up. And you can see here in serial x-rays of the same patient, Week 6, Month 3, and by Month 6, you can see coarse intertubercular bone that was confirmed by the core lab in this indicated healed fracture.

In terms of the X-STOP dislodgment and migration, clearly 30% were complete dislodgments in the X-STOP group. The mean migrations are seen up here. And, again, this

was in two-thirds of the incidences a fairly acute phenomenon. It was seen by the 6-week x-ray.

So, in summary, these incidences, these radiographic observations, the majority occurred acutely. In terms of the location, in the Superion it was coincident with the device; in the X-STOP the majority were anterior to the device. Fracture healing was seen in a significant proportion of patients, and many of the X-STOP fractures also showed device dislodgments or migrations, the overlap phenomenon.

Next, I would like to talk about clinical outcomes. And as a surgeon, I would certainly want to know how these radiographic observations affected my patients.

The next series of charts are going to show on the Y-axis the percent of patients achieving clinical success. And this was the primary ZCQ endpoint, this chart, and this shows all radiographic observations, and you can see that there is no clinical effect on the outcomes in both cohorts in ZCQ, with and without fracture.

In terms of pain and function, this is Oswestry and VAS back and leg. You can see that the Superion results maintained no clinical effect, whereas the VAS back pain did show a statistically significant increase in the X-STOP patients who had radiographic observations.

Now, looking at a more apples-to-apples comparison, we just pulled out the fractures in both groups. Obviously, the Superion group stays the same because they were just fractures, and you can see that the ZCQ scores did show a trend, but no statistical significance in the X-STOP. But if we go back to VAS back, you lose the statistical significance of increased back pain, although numerically it's still a phenomenon in the X-STOP fractures.

Finally, if you look at the migration and dislodgment -- and the reason we're just showing one graph here is because it only occurred in X-STOP -- you can see the statistical significant increase in VAS back returns in those patients with the migrations and dislodgments in the X-STOP cohort.

This is an important slide. In terms of additional treatments, you can see that the radiographic observations did not result in a greater number of additional treatments in either group, and this is really consistent with best orthopedic-neurosurgical spine practice in that we're not going to treat x-rays, we're going to treat the patients. And if they didn't demonstrate a clinical effect from a radiographic observation, it wouldn't make us intervene in that circumstance for an asymptomatic fracture or dislocation.

The FDA has also asked about the mechanism of action in these fracture patients. And because of the lack of clinical sequelae, we did investigate the effect of the fracture on the mechanism of action, and this was again done with the help of Medical Metrics. So we're presenting here in this slide some range of motion data, and this is the decrease in range of motion in both cohorts, comparing preop to postop, and this validates the mechanism of action, which has previously been discussed, as an extension blocker. So, with no fracture, you can see that that extension blocking decrease in range of motion is maintained. With the fracture, you can see in the Superion group that the mechanism of action is preserved. In the X-STOP group, where the fractures are sometimes and not infrequently associated with migrations or dislodgments, you can see that you lose that biomechanical effect. This is a very important slide.

So we asked Medical Metrics to provide some more diagrammatic examples. And

this was made from a Superion case, and this shows the Superion device in appropriate position. This shows the typical fracture coincident with the device. And you can see here how the Superion, when it does not migrate, which it didn't in the study, maintains some contact with the bone potentially. It's held in place with the soft tissues as well, because there's less soft tissue disruption in terms of placing this device and the biomechanical effect of extension blocking can be maintained.

So, to summarize these findings, in the cohorts, there was no effect of pain and function or additional treatment in patients with and without fracture. There is a statistically significant difference in VAS back pain in the X-STOP group. And we do feel that the mechanism of action is preserved due to the stable Superion positioning, lack of migration, and the fracture location, which is typically coincident with the device.

Finally, we undertook to investigate potential risk factors, basically what we learned from the study.

So, in looking at the demographic features, the only features that seem to correlate with an increased risk of fracture would be the younger patients and patients that had a higher BMI. We saw this same finding in the migrations and dislodgments, and these are really not unexpected trends. Younger patients tend to be a bit more active, and patients with a higher BMI would stress the device and the anatomy more.

Looking at some other factors, we found a modest increase in the risk of fracture in patients with the so-called kissing spinous processes and in the Grade 1 spondylolisthesis compared to no spondylolisthesis. An interesting finding was, though, the odds ratios were even increased more nominally in patients with a smaller spinous process, a shorter one,

and the cutoff seemed to be at about 21 mm.

In addition, we looked at one level versus two level, and there was a modest increase in two-level patients with the risk of fracture or device dislodgment. And the most interesting finding was where you put the device. So, if the device is placed shallow, more posterior, further away from the business end of the spinous process, the risk of spinous process fracture or dislodgment and migration increases fourfold. And this is a technical issue that certainly could be mitigated through physician and surgeon education.

So, to summarize, the primary spinous process fracture risk factors includes shallow positioning and the height of the spinous processes. These were the most prominent findings. Similar risk factors for migration and dislodgment. And we do feel that these risk factors could be mitigated through (1) surgeon training and (2) proper sensitivity to patient demographics and anatomy. And to reiterate, the spinous process fractures were not correlated with the clinical outcomes.

Thank you. And I'll turn the podium back to Dr. Nunley.

DR. NUNLEY: Thank you, Scott.

Hello again. Pierce Nunley, for the record. I would like to now discuss the risk-benefit profile of the Superion device as well as the interspinous process devices.

When we look at the benefits of Superion, it's indicated for the treatment of moderate stenosis, and it has demonstrated clinical benefits through 24 but also, as we've seen, through 36 months with good durability. It has also continued to reduce range of motion through its extension blocking mechanism. It's a less invasive surgical approach that does preserve the surrounding anatomy, and it has not demonstrated any risk of migrations

or dislodgments.

So, overall, the results of the clinical study demonstrate that Superion does have a reasonable assurance of safety and effectiveness for moderate stenosis and is a valid option for the treatment of patients with moderate stenosis.

From a safety perspective, Superion has demonstrated that it does have a similar risk profile to that of X-STOP. Its adverse event profile showed similar rates of device- and procedure-related adverse events and also similarly low SAE events. Radiographic observations, yes, there are slightly higher rates of spinous process fractures, but as we've demonstrated, there are no migrations or dislodgments, which have been shown to be related to patient sequelae. And, finally, we further believe that these risks, as has been presented before, and Dr. Blumenthal stated, can be mitigated by surgeon training and by appropriate labeling.

Spinous process fractures are a demonstrated complication of posterior devices that require really careful evaluation, and both the Agency and we have spent quite a bit of time and energy looking into that, to try to glean as much information as we can. The FDA has referenced articles on this, but unfortunately the best that we have for the literature out there tends to lack in quality of comparative data. They are low sample size, typically single arm and dissimilar patient population, which I think is one of the most key factors, and are we comparing apples to apples as far as comparing these patient populations and studies? And also there's a significant amount of off-label use, which again brings in a bad bias, which I think we need to be careful. So, really, the best means of comparison is the Level I evidence before us today and before the Agency before, and some of the articles that are

Level I evidence that we've reviewed.

Some of these limitations, as we go into this a little in more depth, is the Bowers paper. They show a 23% spinous process fracture rate, but this is in a 13-patient population, so it doesn't take one or two patients to swing that number significantly, obviously. But, more importantly, greater than two-thirds of the patients in this study were severe stenosis, and as we've stated previously, one of our concerns is kissing spine, and kissing spine is noted much more frequently in patients with severe stenosis. So I think this is quite skewed.

If you look at Kim's paper, it does have 38 patients, and they did note a high fracture rate of 28.9%, and they performed CT in all of those patients in order to pick up that rate; 11.2% percent were considered to be symptomatic. So like we've discovered here, not a large percentage were symptomatic. But another problematic part of this study is that they used the LANX ASPEN system, which is not again on label for this.

And, further, I think we need to discuss the fact that it seems that the Agency, because of the way the article was written, relied heavily on this article, 38 patients, to suggest CTs for ongoing studies. And we're somewhat concerned about that because, as we've shown, these are mostly symptomatic, and most of the time the reason for getting a CT scan will be because we're going to do something to alter the treatment and it will have a treatment effect on the patients. So I think we need to carefully work together for what's best for the patient and those recommendations.

Barbagallo in 2009, a larger study, it was 69 patients, and it showed a relatively smaller fracture rate, but a high revision rate for those with fractures. But a problem with

this study was again it was a mixed population and really isn't quite the same patient that we were treating.

And then, finally, Moojen in the 2015 recently published article. It was an interesting read with coflex, but it was with and without a decompression. So, of course, without a decompression, that would be off label. They noted a low spinous process fracture rate, however.

So, on whole, these FDA -- these studies that were cited by the FDA are small-scale investigations, they primarily lack control groups, and they're rather low on quality. While it's important to present these findings, we still feel that the Level I clinical evidence that's before us with the study here and the coflex study is probably a little bit of a higher value.

And digging down into that a little bit more and trying to compare the Superion to other available treatments, when we combine and look at the data from the coflex study, we have over 700 patients that are Level I study patients. The other issue is that both of these studies used the same laboratory with the same techniques to identify these spinous process fractures and radiological events. And in the coflex study they also noted that 75% of the patients were asymptomatic.

Interestingly enough, there's a high fracture healing rate in all of these studies. And even more interestingly, in the control arm of the coflex study, that was a posterior lateral effusion. There was still a 12% spinous process fracture rate, which if we think that spinous process fractures occur because there's an interspinous process device, that would kind of cause us to question a little bit of why that is. So this is a little bit more complicated than simply a device placed in the interspinous region. So, again, I think the Level I clinical data

does show a lack of clinical sequelae of the spinous process fractures in general.

So when we evaluate the risk-benefit profile of these devices, we see the following. There's a relative efficacy. We've seen real-world success that's based on leg pain relief. We've also seen comparative improvements versus direct decompression. The perioperative metrics are favorable for this indirect approach. And also the postoperative complications have been favorable as well, showing significantly less procedure-related complications.

And then on the reops and revisions, it's true that indirect decompression, it doesn't limit as much our future surgical options. And reoperations are really more a treatment of advancement of disease, and more importantly, they're not safety driven; we're not removing the device because of a safety concern. So from a risk-benefit profile standpoint, we believe that that is supported by the Level I evidence in front of us.

The FDA has asked us to compare Superion to other treatments, and while this is difficult to do, we tried to pull together reasonable articles to do this. So the spectrum, as I discussed earlier in my presentation, of least invasive to most invasive, we thought, let's look at epidural steroid injection.

Manchikanti actually has a Level I evidence, prospective, randomized study that was published in 2012 on epidural steroid injections and in that found 44% of the patients at 2 years -- and this is a 2-year leg pain study -- did have maintenance of improvement, which for an injection actually is pretty good. But when we look at our PMA study, we have 76% maintenance at 2 years. And looking at four good quality, potentially, articles of the *Spine Journal*, we find that for laminectomy, those results are either comparable or less than

those of Superion.

And digging in a little bit deeper, if we look at ZCQ scores that were published on the Stromqvist, Lonne, and the Davis studies and compare those side by side with the Superion, we noticed a few things. One is that the entrance baseline does show a fairly good clumping of the severity of patients going into these studies, and we notice improvement in all of these studies. And we also notice that they tend to clump again, at the end, in a reasonable fashion, thus showing that we tend to be at least comparable in ZCQ symptom severity and physical function.

Regarding perioperative outcomes, it's really one of the major benefits of indirect decompression. And, again, we're showing this in combination with the coflex IDE, which is a fairly good comparison. While the indicated populations are slightly different, this data does have quite good comparisons, and the operative time is half that of a decompression and a third of that of fusion, and blood loss is minimal in the Superion compared to either decompression coflex or decompression and fusion. And the hospital length of stay is at least comparable, if not better. So indirect decompression is associated with more favorable perioperative metrics.

Another major benefit of decompression compared to direct decompression is looking at perioperative risks. This large-scale published analysis of the Medicare data does show a lower rate of wound complications, life-threatening complications, and re-hospitalization for interspinous process patients, compared with direct decompressive surgery. As we see here, even wound complications, if you look at that being 1% or less, moving that needle as far as millions of patients, it doesn't take long to understand that

that has a major impact. One percent doesn't sound like much, but it is truly a major impact on patient care and even on the cost to society and the healthcare system as a whole. So I think that that's important to look at these. And certainly Superion is associated with an interspinous process. Devices are associated with fewer postoperative complications.

So when we look further in the scientific basis and the comparison of treatments, the FDA cited some safety and efficacy information in articles in the literature as definitive of this class of devices. And much of the information provides some difficulty for comparison for this IDE study, due to the nature of the studies being outside the United States and not really in the same stringency of the IDE that we do here. In other words, these studies are often different patient populations, low sample size, and do not have controls. And while these papers are the only published treatments, we really need to weigh carefully looking at this data versus the Level I data that is before us.

Now, let's talk a little bit about the indirect decompression and reoperation rates and options, because I think that's important to understand what we're talking about. So, if we do an indirect decompression on a patient and we note that through this study and previous studies there tends be an 80% success rate, so that means 8 out of 10 patients are going to keep the device, but that also means, on the contrary, that 20% will not.

And when that happens in patients in my clinic, then I have a decision to make, and as a surgeon, I'm now looking at do we do other treatments? But now they're failed and the patient wants to have something done. The operations before me now are a virgin decompression, which meaning that the canal has not been opened, the canal is still

pristine or in its disease state, much easier surgery than it would be if I'd already done or somebody else had already done a decompression. And now I'm doing a redo decompression with the scar that's present and the increased complications of a redo decompression, which are dural tears, increased operative time, blood loss, increased risk of nerve damage, and also limiting some of my options potentially, depending on what that is. Or the other option is a virgin decompression and requiring a fusion so the patient demonstrates signs or symptoms that would indicate doing a fusion.

So because of that and because of the risks associated with the benefit of basically how well patients do in the majority and that the salvage part of this surgery is still not a bad option, I really think it should be considered at least as one of the first-line options for patients with moderate stenosis.

Well, if we look at the other side of that, let's say we didn't have interspinous process devices or we elected not to and we did a direct decompression. Well, when we look at the literature and trying to be intellectually honest, it's kind of all over the boards, but it's probably safe to say that the majority of the literature would support a 60% to 80% success rate, long term, of decompressive procedures. So there's a complication rate still associated with decompression, and that is typically in the 7% to 9% range.

Well, if a decompression procedure is ineffective, then we have other options which are really less than desirable than the other options of a failure of an indirect decompression, and those are pain management for our patients, which is long term and quite costly, not just to the patient but also to society. And then doing an extended decompression, which I discussed earlier, is a much more difficult procedure and also the

fact that we may need to do a fusion. And if we're going to do a fusion, now we're doing a fusion where there's already been a decompression, which depending on how we choose to do that fusion may cause us to have to do a different procedure than we want to or at the very least make it more difficult. And, more importantly, there's readmission rates that are significant for these larger procedures and reoperation rates that are quite high for redo procedures.

So, in summary, the benefits from a risk standpoint of Superion are that it's a less invasive approach. We demonstrated that it has fewer postoperative complications. It also demonstrates clinical benefits not only through the 24 months that was original study, but as we've had time and been able to present, 36 months with significant durability of the results at that time.

The risks. The reoperation rates are there, but we noted that there's 80% of the patients who do not require a subsequent reoperation. The spinous process fractures are an issue that we've discussed at length today, but we demonstrated that through this study and other Level I clinical evidence, that for the majority they're asymptomatic and that there is a high healing rate for these fractures.

Also, from a risk mitigation standpoint, we do believe that labeling modifications will mitigate these risks significantly and that surgeon training and not only that but optimized patient selection and device placement will also help mitigate these. Further, by continuing our investigation in the post-approval studies, we feel that we can show this.

The post-approval study considerations that we've placed and had conversations in front of the FDA are twofold. One is a continuation of the current study and following these

patients out to 5 years. There has been a proposal to potentially use CTs for this part of the study, and as has been stated multiple times in our presentation, we have some significant concerns about that, and they're really patient concerns. I know personally dealing with IRBs with other studies, justification of CTs is a very sticky wicket, and as a PI, I have to go in front of the IRB and justify why we are doing that. And I think, with the data that we have before us, it would be a difficult uphill battle to justify that to my IRB, the ones that I've used to do this, unless we can find where there's a patient safety issue or there's a treatment option that's going to change. But we do look forward to discussing this with the FDA as we go forward and ultimately doing what's right for the patients.

The second study that we've proposed is that of a decompression control, which is a very interesting study, and quite frankly, early on was one of the options, but the FDA wanted us to go with the X-STOP because it was the predicate device that was approved and the most similar device and appropriate device for our control. This study would be a 2-year evaluation with a 3-year long-term follow-up. And again they proposed CTs, and I've said before, we need to work through that for what's best for our patients.

So we believe that the actual condition of use study will validate the risk measures, and we think that it will actually show that this, in fact, will decrease some of the problems that we've seen with this study.

With that, I thank you for your time and attention, and most importantly, I do thank you. And on behalf of VertiFlex, thank you for your service on this Panel. As a fellow clinician, thank you.

And I'd like to bring Mr. Fender back up, and he would like to close the remarks for

the Panel. Thank you very much.

MR. FENDER: Thank you, Dr. Nunley. And for the record I am Earl Fender, CEO of VertiFlex.

I'd like to summarize the conclusions of the trial, which is repetitive from what you've heard. But I'd also thank, genuinely, the Panel and the Agency for the hard work and the preparation that you did for getting ready for today, as well as your participation today.

As an aside, I know you can appreciate this is a big day for a small company like VertiFlex. We're at 7 years and counting in this trial, and as I said at the outset, we genuinely want to present the data and give you every chance to look at it and make your recommendations.

In substantiating the trial design, I know you heard over and over again that we believe we have studied the correct stenosis population, one that's more oriented to moderate stenosis versus later stage, and we've used the right control in this trial.

Success was achieved in the primary endpoint. Complex or not, that was the endpoint of the trial, and we've exceeded the posterior probability of success achieving non-inferiority, and we feel that the 7 years of work in this trial have paid off with those kind of results.

You heard now 10 times that while the success rate in the trial and this composite endpoint was over 50%, we're pressing that clinical success was over 80%. And that's important because when you look at some of the other literature, when you look at the laminectomy chart that Dr. Nunley showed just a while ago with the four studies that were published in *Spine*, the clinical success rate is really what we're looking for. How do we

treat patients, what are their outcomes, and how do they feel about the treatment that we gave them?

In terms of summarizing radiographic observations, yes, indeed, clinical sequelae was generally lacking in this. It doesn't mean that we don't take those fractures seriously, and that while we've, as you've seen, assessed the risks of why these fractures can happen, that's a good reason why we believe that a combination of labeling and good, solid surgeon training and patient selection will give the best chance of reducing these fractures post-commercialization.

It's interesting. One of the pieces of data that you saw in the coflex trial is the fusion fracture rate; it was just over 12% and actually slightly higher than Superion experienced in this trial. We also talked about that while spinous process fractures were an issue for Superion, we experienced no migrations or dislodgments. And, as you saw, the data demonstrated that there's a higher rate of axial back pain in patients if there's a migration and dislodgment.

Overall, I think that we've demonstrated a positive risk-benefit profile. We summarized safety and effectiveness of Superion and I think, importantly, established the durability of the product out to 36 months, also with a very high follow-up rate of patients. The 36-month data, we think, validates the robustness of the data for this device and validates and perhaps indicates that Superion can be at least a good treatment option for lumbar stenosis in a certain select group of patients.

So, with all of that in mind, we respectfully ask for the Panel's consideration and support as we approach this PMA process for the rest of the day.

Thank you very much.

DR. RAO: I'd like to thank the Sponsor's representatives for their presentation.

Does anyone on the Panel have a brief clarifying question for the Sponsor? Please remember that the Panel may also ask the Sponsor questions during the Panel deliberation session later on after lunch. But if you have any brief clarifying questions, please raise your hand and go ahead.

DR. HAINES: Yes. I've searched in vain for the documentation of the selection of the clinical significance change on the Zurich Claudication Questionnaire, and if somebody could provide a reference for that, it would be helpful.

MR. STIEGMAN: Sure, we'll provide that momentarily. I'm Glenn.

DR. RAO: Dr. Yang.

DR. YANG: So I have two questions. One is about, on page 32, your protocol violators. I think I read somewhere that some of these implants were placed along with some facet trimming and et cetera, et cetera. So I take it that all of those were included in the violators and excluded from the analysis?

MR. STIEGMAN: They were included in the analysis if they didn't meet the definition and the inclusion criteria. So the inclusion criteria did have the ability to clear out soft tissue, as long as they weren't decompressing the spine. So they were included in the intent-to-treat group. Is that what your question was?

DR. YANG: Yes. I thought I read somewhere that they were more extensive, though, that there was actually burn down at the facet joint and --

MR. STIEGMAN: We have a couple of slides on that, and we can present that later.

DR. YANG: Okay.

MR. STIEGMAN: If that's okay.

DR. YANG: I defer that to Dr. Rao.

DR. RAO: That should be fine.

MR. STIEGMAN: Okay.

DR. YANG: Okay. And can I ask a second question?

DR. RAO: Go ahead.

DR. YANG: Okay. The next is the timing of the x-rays. Were any of the fractures -- on page 62 I think it is. Your groupings are postop to Week 6 and then Month 3 to 12 months. Were any of the fractures coincident with the placement? I know you can see it on the fluoro; it fractured right away.

MR. STIEGMAN: If they saw a fracture intraoperatively during the placement, it was usually noted as an AE. And MMI got all images anyway, so they noted that fracture as well.

DR. YANG: Right. My question was were there any?

MR. STIEGMAN: Yes.

DR. YANG: There were?

MR. STIEGMAN: Yeah. During the procedure itself?

DR. YANG: Yes.

MR. STIEGMAN: Yes.

DR. YANG: And how many of those -- were they counted in this postop to Week 6 group?

MR. STIEGMAN: Yes.

DR. YANG: And how many of them were there?

MR. STIEGMAN: I'd have to look at the table. I can get that for you, though.

DR. YANG: Okay. And also one last thing.

MR. STIEGMAN: Um-hum.

DR. YANG: The fractures. Were they through and through? Because I'm looking at page 76, and it's interesting that the X-STOP ones had an increase in ROM, but the Superion ones did not. So there must be something different there. So, with your fractures, were they through-and-through spinous process, or were they just sort of halfway, a little bit cracked?

MR. STIEGMAN: We really believe -- and we can present more information in a slide on this, as well -- that due to location of the placement of each device and the fact that we know that some of these devices migrated, the X-STOP side, that that's why you see that inability to maintain the blocking.

DR. YANG: Okay. So we'll have more information on that.

MR. STIEGMAN: Yeah, we can present that as well.

DR. RAO: Thank you, Dr. Yang.

I just have a quick clarifying question. Your proposal lists the inclusion criteria as L1 to L5. Does that mean that the device is not indicated for the L5-S1 motion segment?

MR. STIEGMAN: Correct.

DR. RAO: Dr. Golish.

DR. GOLISH: Since the choice of the non-inferiority margin is central to any two-arm non-inferiority trial, could you tell us very concisely how you arrived at that number, 10%?

MR. STIEGMAN: This is Glenn Stiegman.

Ten percent is a common delta often used in spine studies. It's generated in collaboration with the FDA.

DR. RAO: Dr. Lyman.

DR. LYMAN: I wanted to follow up on Dr. Haines' question. And I did a little bit of your work for you. I tried to find that MCIC -- MCID of 0.5 and 2.5 and it looks like the references for that, at least in the literature, are from the mid-'90s in Switzerland, so these measurements are usually determined based on study populations. And so I'm guessing that those patients aren't necessarily representative of the patients that you end up enrolling in your trial. So I'm wondering if you did any evaluation of what your internal clinically important difference or change was.

MR. STIEGMAN: This is Glenn.

I will have to get back to you on that. I know that the 0.5 clinically significant improvement has been used in several other studies, for the X-STOP study, for the coflex study, for a spinal stenosis population, and it's well accepted, I believe, in industry. If you look at the slide now, the Tully article also validates the two out of three criteria that was utilized as the primary endpoint.

DR. RAO: Dr. O'Brien. Mr. O'Brien.

MR. O'BRIEN: We got into the characterization of the fractures for Superion. I just am trying to compare Slide 63 with Slide 78. They appear to me to be two different characters of fractures. Which one of those really represents the fractures that Superion had on average?

MR. STIEGMAN: I'm going to pull up the slide real fast.

MR. O'BRIEN: And with that question, just for my understanding -- I haven't seen the device itself. What is actually holding that onto the spinous process?

MR. STIEGMAN: Well, it does have the four wings, the two on either side, but it's gravity, weight.

MR. O'BRIEN: It's gravity and weight.

MR. STIEGMAN: You put it in there in a slightly distracted manner so it has some compression from the top and bottom so it stays in place.

MR. O'BRIEN: So being gravity fed, the nature of the fracture could make a difference in terms of what happens to the device ultimately?

MR. STIEGMAN: Ultimately, yes.

MR. O'BRIEN: Okay.

DR. RAO: Dr. Trier, please.

DR. TRIER: Dr. Trier.

To follow on with Mr. O'Brien's question, it would be helpful to me to understand, and potentially to the Panel to understand, the actual design of the device and what you found that was holding that device in. I mean, obviously, there were no migrations. So you know, what was holding that device in? I know one of your presenters said something about soft tissue. So, if you could provide more information about that, why the device did not migrate with those fractures.

MR. STIEGMAN: Um-hum. Yeah, we have a couple of slides, backup slides, that we can present that information as well.

DR. RAO: Dr. Graf.

DR. GRAF: One follow-up question on the proposed studies, post-approval studies. Your Study 2, the actual conditions of use, proposed a decompression control. Does your indications for the product include a spondylolisthesis subset of that or just spinal stenosis itself?

MR. STIEGMAN: I think that's an ongoing discussion and negotiation with the FDA, to specifically define that population since, as Dr. Nunley stated, the decompression population can be much larger than the population for this particular device.

DR. RAO: Dr. Gilbert.

DR. GILBERT: I think it was Mr. Reitzler who indicated that there is an optional burring that can occur to the spinous process during insertion, and I'm wondering if that has been looked at as a correlate to fracture. So were the spinous process fractures occurring predominantly in burred cases or in un-burred cases, and do you know that?

MR. STIEGMAN: The incidence of burring was not collected unless the surgeon specifically wrote that down on the case report form, so we were unable to do that analysis.

DR. RAO: I just have some follow-up questions on this L5-S1 motion segment issue. Do we have information -- you know, we all are aware that the S1 spinous process can be very attenuated and can be redundant. Do we have information on the X-STOP, whether their dislodgments occurred mostly at L5-S1 or whether they occurred more proximally in the lumbar spine? Because it seems like if you were not going to do L5-S1 with your device and you're comparing it to a group where it was done, then that might skew the results to some degree. So you may or may not have information on that right now, but if you could

kind of clarify that for us, that would be great.

MR. STIEGMAN: Dr. Blumenthal will help address that.

DR. BLUMENTHAL: Scott Blumenthal.

L5-S1, in our study, was excluded as the previous devices, both the X-STOP and the coflex, are not indicated for use at L5-S1, so there won't be any of those in the study. And if there was, it would be a protocol violation. As you pointed out, the spinous process of S1 is usually quite minimal, and it's sloped more severely so that it usually doesn't -- it wouldn't be technically possible to support an interspinous device, and if you put one in at 5, well, you'd almost expect it to come out.

DR. RAO: But that still doesn't give us information on whether any of those -- so your X-STOPs did not include L5-S1?

DR. BLUMENTHAL: Correct. L5-S1 was a contraindication for this study as it was for the X-STOP study.

DR. RAO: Thank you. That explains things.

Mr. O'Brien.

MR. O'BRIEN: Sorry, just one last question. Regarding reoperation rates, looking at Slide 99, with looking at the literature and indicating a 60% to 80% success rate for direct decompression -- and I just wanted to know if you could comment. In Deyo et al. in 2013 they did a retrospective cohort analysis. That seemed to indicate that interspinous processes would have -- you know, certainly complications were much better. On the other hand, reoperation rates were almost double with 16.7 versus 8-point something, et cetera, depending on whether it was fusion or non-fusion. I just wondered if you could comment

on that because it doesn't seem to be included here.

MR. STIEGMAN: We'll get back to you on that one.

DR. RAO: Dr. Graf.

DR. GRAF: Just a follow-up on that as well. I don't really know -- I'm at page 98 -- if that's a fair comparison to compare the revision of your product to a revision laminectomy because the endpoint would be a spinal decompression. So you're comparing a spinal segment that's already been decompressed through a revision of removing your product, which the spinal canal has not been directly decompressed. That was mentioned, and I don't think that's a fair comparison, just for reference.

MR. STIEGMAN: Okay.

DR. RAO: I have another question for the Sponsor. It's a little unclear when I read the proposal that was submitted -- that was sent to us earlier -- and when I listened to your presentation today, it's a little unclear exactly which fracture number you're using in your calculation of non-inferiority. The proposal lists the clinical investigators' number of fractures, which I think was 21. Today I heard the 31 number, which was also listed in the proposal, but which was the independent number of fractures. And then I also heard -- I think it was your presentation that talked about just the non-healed fractures being considered for non-inferiority.

So which number are you using? Is there a change in your design of the study and the proposal that was submitted to the FDA? And could you explain your rationale for the change?

MR. STIEGMAN: This is Glenn.

I'll go backwards to forwards. There was no change in the design of the study. The fracture rate that was used was the one by the independent core lab, MMI. The 21 represents those fractures that were not healed at Month 24. The 31 is the total fracture rate regardless of healing or not.

DR. RAO: So which number did you use for the non-inferiority that was in the proposal that was sent to us? And is there a different number today?

MR. STIEGMAN: There's not a different number; it's 21.

DR. RAO: Thank you.

Dr. Lyman.

DR. LYMAN: So you've expressed that you think that the fractures were -- didn't result in disability based on your patient-reported outcome measures, and I believe you looked at the 24-month follow-up time point. I'm wondering how distant -- I mean that was at least a year after the fracture was identified, right, because I think most of the fractures were during the first 12 months. I'm wondering if you looked at the scores more proximal to the fracture, after the fracture had occurred, whether or not the patients were symptomatic at that time point rather than at the 2-year time point.

And a follow-on to that is you expressed again, based on your MCID, the percent of patients who achieved an important change or important difference, but we don't see for the fractures versus non-fractures the summary statistics around those scores. It may be that the patients achieved that change, but they still had lower outcome scores than the patients who didn't have fractures. It would be interesting to see that information.

MR. STIEGMAN: We'll certainly present that.

DR. LYMAN: Great. Thank you.

DR. RAO: Dr. Carrino.

DR. CARRINO: In the exclusion criteria on Slide 23, it states a significant instability, and I just wanted to know how that was defined.

DR. BLUMENTHAL: This is Scott Blumenthal.

Significant instability would be a change in positioning on flexion. We did preoperative flexion-extension x-rays. So, if it was a stable spondylolisthesis up to Grade 1 without change on flexion-extension, that was considered a stable. And then if it moved on flexion-extension, that was unstable and considered a contraindication.

DR. CARRINO: So just to clarify. Any movement, 1 mm, 2 mm, 3 mm, 4 mm, translation, angulation --

DR. BLUMENTHAL: Three millimeters.

DR. CARRINO: Three millimeters, okay. And those radiographs were done upright, recumbent?

DR. BLUMENTHAL: Upright.

DR. CARRINO: Okay, perfect. Great. Thank you.

DR. RAO: Another question, Dr. Blumenthal. Maybe it's good that you're at the microphone because this is kind of a clinically oriented question.

We're trying to kind of figure out non-inferiority between two groups that are relatively close, so little changes in numbers here and there may affect the outcome potentially. I'm still trying to understand your rationale for the use of the 21 number for spinous process fractures. I think most of us will agree with you that the fracture itself is

not a clinically relevant issue, which is what you've stated in your proposal. The fact that a spinous process fracture occurs is not devastating to the patient. They usually tend to be painless, like in your proposal. The reason the fracture happens sometimes is because of the stresses between the spinous processes by the spacer, is my theory anyway. So when the fracture happens, the bone displaces a little bit and the posterior disc height and foraminal height settles a little bit.

You've talked in your proposal about the differences between your study and the original X-STOP IDE, and you've pointed out that one of the differences was you didn't measure maintained distraction. From a clinical standpoint, I'm not sure that the fracture itself is that relevant, but the fracture indicating that there's some loss of height is relevant to us. You measured some of these numbers, I think, but they weren't presented to us either in the proposal or today.

Would you be able to, maybe this afternoon, give us information on the posterior disc height originally, posterior disc height at the end of 24 months between the two groups, and point out to us whether there were any significant differences in the groups that had fractures and didn't have fractures?

DR. BLUMENTHAL: Yes, we can do that.

DR. RAO: Thank you very much.

Dr. Golish.

DR. GOLISH: This is not really a simple clarifying question, but if I may, Mr. Chairman, I'm hoping that some combination of the Sponsor and FDA this morning will provide a concise but deep summary of the data that resulted in the X-STOP approval,

because though this is not the X-STOP panel, those data are central to the foundation upon which the non-inferiority design we're considering today is built. So, in 2005, 191 patients in a two-arm superiority trial looked like very compelling data for the X-STOP. Seen through the lens of 10 years of clinical experience, it seems, in retrospect, those have any number of issues. So it would be important for us to look at that because it's central to the argument.

DR. RAO: Dr. Trier.

DR. TRIER: Dr. Trier speaking.

And I understand your comment, Dr. Golish, about the use of the X-STOP. But as an Industry Representative, I do need to at least say -- at least caution the Panel about the negotiations that go on between FDA and industry in identifying what should be a comparator for a control group for an IDE of this type.

So, as industry sits here and thinks about how we interact with FDA, you know there's always a negotiation and there's always an agreement about what that study is. It's a significant investment on the part of industry as well as FDA getting to this point. So I guess I would just caution concerns about looking at the comparator for this study.

DR. RAO: Thank you.

One more question, Dr. Blumenthal. I haven't heard this term for a while, but Dr. Nunley talked about a sticky wicket. For a non-cricket playing person, that's a good one.

(Laughter.)

DR. RAO: But it's a little bit of a sticky wicket. Dr. Nunley mentioned the indications for the procedure as being a patient who gets relief with flexion. But, then again, when we talk about the mechanism of action of the device, we're talking about an extension blocker.

So we have two slightly different aspects of the lumbar spine range of motion, and you haven't given us information that I could find on exactly how much extension is being blocked or how much flexion there was as opposed to total range of motion.

So, if a patient gets relief in flexion, that aspect of the patient's symptomatology would in theory not be relieved by this device, if that's my understanding; whereas if a patient gets exacerbation with extension, that in theory would be relieved by this device. But we don't have range of motion data on exactly how much of that arc of motion was flexion and extension, how much was lost or preserved after insertion of the device, and how much the patient had originally that may have contributed to their symptoms.

DR. BLUMENTHAL: A great question, and we discussed it extensively. The data that I presented was total range of motion, and to be able to isolate just extension and just flexion would have required -- as you know, everybody's neutral spine is a little bit different, and particularly a degenerative spine is different than a young spine. So we didn't feel that there was a good way to be able to find a comparable neutral position that would be measurable between patients. So we measured total range of motion, and that's what I presented, but it's that neutral that's very hard to define between a very diverse patient group.

The other question regarding the clinical presentation, again, the clinical presentation of stenosis, as we all know, is pain with ambulation relieved with some type of forward bending, sitting, et cetera, et cetera. And that was the most reliable thing we could use clinically, to the investigators, to have as much of a homogeneous clinical patient group as possible.

DR. RAO: Thank you.

Ms. Harmon.

MS. HARMON: Hi. Monica Harmon, Consumer Representative.

I just have a question in terms of patient outcomes and satisfaction, I think, perioperatively, that is before, during, and after the procedure. At one point in your presentation, it talked about surgeon training and labeling. Can you speak more to what that training would actually look like?

MR. STIEGMAN: Sure. This is Glenn Stiegman.

This will be a negotiation process with the FDA. We want to ensure that the surgeons and the users in the future, hopefully post-approval, are sensitive to the risk factors of spinous process fractures. And whether that includes didactic-type scenarios or cadaver testing, we're working in hand with the FDA to make sure that all surgeons are adequately trained.

MS. HARMON: And how does that look for the rest of the team working with the patients? You know, you talk about the surgeons, but what about the nurses?

MR. STIEGMAN: Yes, everyone.

MS. HARMON: What about the discharge planners, all of that?

MR. STIEGMAN: Yes, we've talked regimen, nurses, the whole clinical team.

MS. HARMON: Okay.

MR. STIEGMAN: Definitely.

MS. HARMON: And in terms of patient education, have you thought about literacy levels of patients, the family, the support systems?

MR. STIEGMAN: Yes, ma'am, all of the patient labeling is written in a language that everyone should be able to understand. And, again, we're in the process with the FDA to work through the ability to communicate effectively to all types of patients.

MS. HARMON: Thank you.

DR. RAO: Dr. Alander.

DR. ALANDER: Yes. I'd like to reference Dr. Rao's question in the aspect of sagittal balance, and I don't see anything in the study here that would look at whether or not sagittal balance was used or referenced with regards to indications and how that might affect your indications.

MR. STIEGMAN: We'll investigate that further and get back to you.

DR. RAO: Dr. Gilbert.

DR. GILBERT: So I'm going to shift gears just a little bit. And Dr. Trier mentioned this earlier, about not having a good sense of the geometry of the device and in particular the contacting location between the device and the spinous process. The spinous process is a very sharp radius, as I understand, in that location, and the titanium is a wider U shape. But your contact area between the two parts is very small and could be very variable, which could lead to higher stresses and greater risk of fracture, and I'm wondering what you've done, either preclinically or otherwise, to assess that contact region between bone and device.

MR. STIEGMAN: I think, in conjunction with Dr. Trier's question, we'll present something a little bit later.

DR. RAO: Mr. O'Brien, you had a question?

MR. O'BRIEN: Yes, one on the flexion-extension. And you had data that compared the range compared to the X-STOP, but I was wondering if you had data that compared it to decompression.

MR. STIEGMAN: No, but that would be something interesting to look at in our post-approval study.

MR. O'BRIEN: Secondarily, I just wanted to refer to the comment made by Dr. Golish, in terms of looking at the X-STOP data which is used as the benchmark for the study, and notwithstanding -- and I respect Dr. Trier's point about the negotiations, et cetera, but from a patient perspective, I am very interested to see how that relates to it. And certainly over 40 years I've seen that we've changed a lot of what we do and don't do and what we use as benchmarks. So I think it is important and relative to the discussion.

DR. RAO: Thank you very much. We'd like to thank the Sponsors again and thank the Panel for their attention and clear questions.

It is now 9:58. We will take a 12-minute break, get back in the room at 10:10 and try and get started on time. Thank you very much. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 10:10. Thank you.

(Off the record at 9:58 a.m.)

(On the record at 10:10 a.m.)

DR. RAO: Thank you all again. It is now 10:10, and I would like to call this meeting back to order.

One brief announcement before we get started. Dr. Kathleen Propert was a Panel

member -- supposed to be a Panel member for this morning's session but was unfortunately unable to make it to the meeting.

The FDA will now give their presentation.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The FDA will also have 90 minutes to present, and if they get done earlier, then we will move the schedule forward. FDA, you may now begin your presentation.

DR. WYATT: Thank you, Dr. Rao.

Good morning, ladies and gentlemen of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee. The following will be the FDA's presentation of the material which is the subject of today's deliberations.

My name is Zane Wyatt, and I am the lead reviewer of the PMA which is under discussion today.

On this slide is the review team which has been instrumental in reviewing and providing comments on the material which you will see covered today and which has been previously provided to you in your preparation materials.

In brief, here is a short overview of the FDA's talk. We will start with an introduction of the device, a clinical background of the disease state, regulatory history of similar devices, and then an overview of the IDE data which is presented here, followed by a review of the post-approval study considerations.

As alluded to before, the purpose of today's meeting of the Orthopaedic Advisory

Committee is to go over the results of the clinical trial which was conducted for the Superion Interspinous Spacer device under IDE G070118, in addition to reviewing the safety and effectiveness data contained in a premarket approval application submitted by VertiFlex, Incorporated.

The Agency has requested this meeting to obtain your expert opinion on six distinct issues which arose during the review of this PMA submission. These issues will be discussed at greater length in this presentation. However, to summarize, the Agency is concerned with an observed spinous process fracture rate which is higher than compared to the non-fusion interspinous devices intended to treat lumbar spinal stenosis observed in the control arm of this study as well as in the literature. It should be noted that these rates were determined based upon independent radiographic review.

And, additionally, the Agency remains uncertain regarding the clinical significance of these observed spinous process fractures, as both the Superion interspinous device and the control device rely on the integrity of the spinous processes to produce their treatment effect.

Thirdly, the Agency is unsure of the sufficiency of the clinical metrics used that have been presented to support the Sponsor's claim that spinous process fractures associated with the Superion ISS are asymptomatic and do not result in clinical sequelae. It is unclear whether the data presented is appropriate and adequate to assess the clinical significance of these spinous process fractures.

Additionally, facet debulking, osteophyte removal, and soft tissue removal were performed during implantation of both devices. As resection of these anatomic structures

could potentially provide for neural structure decompression, the Agency requests input regarding how to differentiate the treatment effect of the device from any potential treatment effect resulting from these interventions.

Although the Superion interspinous device and the control device exhibit similar overall failure rates, the Superion failure rate is driven by spinous process fractures, whereas the control device failure rate is driven by device migrations and dislodgements. It is uncertain whether these events (fractures versus migrations and/or dislodgements) and their clinical sequelae are comparable.

And, lastly, although the overall success rate of the Superion device was non-inferior to the control device, the overall success rate is low for both devices, approximately 50%.

The Agency is therefore requesting Panel input regarding whether the probable benefits outweigh the probable risks for the use of the Superion device in the identified patient population.

Briefly, as was described this morning, the VertiFlex Superion device is a small H-shaped titanium device which sits between the two spinous processes in the lumbar spine.

This device is designed to restrict and/or block extension and prevent the spinal canal, lateral recess, and/or foraminal narrowing that can contribute to symptoms of lumbar stenosis. Potential distraction of the spinous processes is intended to open the spinal canal, neural foramina, and lateral recesses.

Also as mentioned this morning, here is a review of the indications for use of the device.

Based on these indications, the device's intended treatment effect is to mitigate the symptoms of moderate lumbar stenosis and specifically neurogenic intermittent claudication. The device achieves that effect by being placed between the adjacent spinous processes and limiting motion of the spine, i.e., as an extension blocker. Additionally, it is possible for the device to provide indirect decompression, preventing narrowing of the spinal canal and neural foramina.

In review, prior to initiation of the clinical study which was performed, the Sponsor conducted the following nonclinical assessments of the device to establish a baseline measurement of the device's safety. It should be noted here, at this time, that there are no remaining concerns with any of the nonclinical assessments of the device. These nonclinical studies included static and dynamic axial compression of the device, static and dynamic torsion of the device, deployment under load, and additional cadaveric assessments of the mean resultant moment, angular displacement, and overall motion of the spinal segment, in addition to MR compatibility testing.

It is now my pleasure to introduce the lead medical officer for this premarket application, Dr. Elizabeth Panox.

DR. ADEGBOYEGA-PANOX: My name is Elizabeth Panox. I am the medical officer assigned to the Anterior Spine Devices Branch, and I was clinical reviewer for this PMA. I will be covering the clinical background, regulatory history, overview of the IDE study, safety data, and effectiveness data.

As has been mentioned, the Superion device is indicated for the treatment of lumbar spinal stenosis. The next five slides will give an overview of lumbar spinal stenosis, mainly

for the benefit for nonclinical members of the Panel.

Lumbar spinal stenosis is any type of narrowing of the spinal canal, nerve root canals, or intervertebral foramina. The most common type of lumbar spinal stenosis occurs due to acquired degenerative changes involving the intervertebral disc, facet joints, and/or soft tissues of the spinal motion segment. Gradual narrowing of the spinal canal and/or neural foramina leads to compression of neural structures which may or may not be symptomatic. Spinal instability or degenerative spondylolisthesis may develop as a result of the degenerative process. Lumbar spinal stenosis is the most common reason for lumbar spine surgery in adults over the age of 65.

These pictures demonstrate the anatomical contributors to spinal stenosis. On the left, arthritis and hypertrophy of the facet joints reduce disc height and osteophytes. In the picture below, there's hypertrophy of the ligamentum flavum and the herniated disc. The picture on the right demonstrates stenosis with compromise of neural elements.

Clinically, patients present with gradual onset of low back, buttock, thigh, leg or calf pain, and/or neurogenic claudication. Neurogenic claudication refers to symptoms such as pain, numbness, or weakness involving the buttocks or legs on walking or standing that resolves with sitting down or lumbar flexion. Positioning the spine in flexion tends to relieve symptoms as this position increases spinal canal diameter. Positioning the spine in extension, such as standing or walking, exacerbates symptoms as this motion narrows spinal canal dimensions.

Treatment of lumbar spinal stenosis may be nonsurgical or surgical. Nonsurgical options include medications, non-steroidal anti-inflammatory medication, analgesics, oral

steroids, epidural injections, rest, activity modification, exercise, physical therapy, and bracing.

Surgical treatment options include direct decompression, or laminectomy, which results in direct decompression of the neurologic structures; indirect decompression using an approved interspinous process device such as X-STOP; direct spinal decompression in combination with an FDA-approved non-fusion posterior interlaminar stabilization device such as coflex; and direct spinal decompression in combination with spinal fusion plus or minus pedicle screw rod instrumentation or an intervertebral fusion device.

The FDA has approved two non-fusion interspinous process or interlaminar devices. X-STOP was approved in 2004. It is an interspinous process device which is implanted as an alternative to surgical decompression of spinal stenosis at the affected level. In 2011, coflex Interlaminar Technology is an interlaminar stabilization device which is placed after surgical decompression of spinal stenosis at the affected levels.

The Superion study design under IDE G070118 was a multicenter, prospective, randomized, concurrently controlled pivotal study; 442 patients were randomized in a 1:1 ratio; 51 patients were post-consent screen failures; there were 31 clinical centers; and the final tally was 190 Superion patients and 201 control patients.

The purpose of the study was to evaluate the safety and effectiveness of VertiFlex Superion intervertebral spinous system, also to evaluate the ability of the device to serve as an extension blocker and relieve symptoms of moderate spinal lumbar stenosis as evaluated using Zurich Claudication Questionnaire. Secondary assessments of clinical outcomes included Oswestry Disability Index, the Visual Analogue Scale, Short Form Health Survey,

and a patient satisfaction survey. And, finally, to demonstrate non-inferiority of Superion to the control device.

The Sponsor has already mentioned the key inclusion criteria and the key exclusion criteria that would define the patient population.

The Sponsor has clarified that the device is intended for moderate lumbar spinal stenosis and provided the following definition of moderate lumbar spinal stenosis that will be indicated for their device. It's defined as 25% to 50% reduction in lateral/central foramina compared to the adjacent levels with radiographic confirmation of any one of the following:

- Evidence of thecal sac and/or cauda equina compression;
- Evidence of nerve root impingement by either osseous or non-osseous elements; and
- Evidence of hypertrophic facets with canal encroachment.

And the following clinical signs:

- Moderately impaired physical function as defined as a score of greater than or equal to 2.0 of the Zurich Claudication Questionnaire; and
- Ability to sit for 50 minutes without pain and to walk 50 feet or more.

The two study arms were very similar in terms of demographic variables, with the following exceptions:

- There was nominally significant difference in baseline ZCQ Physical Function domain where the control arm had a 0.1 difference greater than Superion arm.

- There were instances where baseline demographics were trending towards significance, which were attributed to Superion arm enrolling more female patients, including overall height and overall weight.

There were no statistically significant differences in operative variables, although there were numerical differences.

There was satisfactory follow-up of both study arms at 24 months. Specifically, 97.3% of Superion subjects and 94.9% of control patients were evaluated for the composite endpoint at 24 months. Additionally, at 36 months there was 90.2% of Superion patients and 91.4% of patients which were evaluated for the composite endpoint.

This slide contains a summary of protocol deviations in the study. There were 43 major protocol deviations in 36 patients. A total of 19 patients (10 Superion and 9 control) were excluded from the per-protocol population. These patients had inclusion/exclusion violations without having received a waiver from the Sponsor. Additionally, there were five informed consent violations and one patient withdrew consent.

Both devices were implanted between the spinous processes at one or two levels. Additional procedures were required in some cases, which may constitute direct decompression. The Superion procedure consisted of a percutaneous or mini-open approach with or without repair of the supraspinous ligament at the conclusion of the implantation of the device. The control procedure consisted of open access, lateral exposure of both sides of the spinous processes, and penetration or removal of a portion of the interspinous ligament.

Patients were evaluated preoperatively for screening and to capture baseline data.

They were also evaluated on the day of operation to capture operative data and assessment of adverse events. They were assessed at discharge with standing A/P and lateral lumbar x-rays, neurologic status, VAS, and adverse events. Full postop evaluations were performed at 6 weeks followed by 3-, 6-, 12-, 18-, and 24-month assessments and annually thereafter. Success was evaluated at 24 months postoperatively.

Both study arms implanted similar numbers of devices at single and two levels. Approximately half of each study arm had single-level implantation and half two-level implantation. All of the control procedures were performed through an open approach. About half of the Superion devices were implanted in a percutaneous approach and the other half through a mini-open approach. The supraspinous ligament was repaired in about half of the Superion subjects. This procedure was not performed in the control patients.

Additional procedures such as debulking of the facets, removal of osteophytes, and soft tissue removals were performed in both arms of the study, but slightly numerically more in the control. These procedures may add some element of direct decompression.

The operative time differed numerically between Superion and control, with Superion having a longer time average of 56.2 minutes and the control averaging 47.2 minutes.

When making a safety assessment, the FDA considers adverse events, reoperations, and neurologic status. Data was evaluated for safety endpoints by an independent clinical events committee using predetermined stopping rules. Safety outcomes were determined by evaluating the type, frequency, severity, and relationship to device of adverse events through the 24-month time period for all subjects. Adverse events were categorized as

implant-related, procedure-related, adjacent level-related, or systemic. All device-related events, major procedure-related, and adjacent level-related events, and therapeutic failures were reported by the site principal investigators and were adjudicated by the independent clinical events committee. Events reported as having unknown or undetermined relationship to the device by the site principal investigators were adjudicated by the clinical events committee.

The FDA recognizes the following categories of subsequent surgical interventions:

- Revision is a procedure that adjusts or in any way modifies or removes part of the original implant configuration, with or without replacement of a component.
- A removal is a procedure where all of the original system configuration is removed with or without replacement.
- A reoperation is any surgical procedure at the involved level that does not include removal, modification, or addition of any components to the system.
- A supplemental fixation is a procedure in which additional instrumentation not under study in the protocol is implanted.

Neurologic success was defined by the presence of no new or worsening neurologic deficit with respect to motor or sensory function.

This slide demonstrates the summary of the adverse events that occurred in the study. In all categories, the rates were similar in the two arms of the study. Importantly, the rates of serious adverse events that were device or procedure related were 21.1% for Superion and 23.4% for the control.

An independent core laboratory evaluated the radiographs and reported on the radiographic findings. In the Superion group, all 31 observations were spinous process fractures. Fractures also occurred in the control arm, but the majority of observations were dislodgments and migrations. Of the 31 fractures observed in the Superion group, 21 had not healed at 24 months. Of the 17 fractures noted in the control group, 10 had not healed at 24 months.

The Agency will be asking the Panel to comment on the radiographic observations and the spinous process fractures in particular.

The diagnosis of spinous process fracture was made using plain radiographs. Radiographs were evaluated by the sites, by the core laboratory, and they were also adjudicated by the clinical events committee. The number of fractures reported differed between these three entities. Specifically, the sites reported 13 fractures in the Superion group in 11 subjects and 10 in the control group. The independent radiographic lab reported 31 fractures in 31 patients in the Superion group, with 17 in the control group. The CEC adjudicated 24 in the Superion group and 14 in the control group. The numbers reported by the core laboratory were used at analysis.

Given these differences, the Panel will be asked for input on the appropriate method of diagnosis of spinous process fractures.

The spinous process fractures are further categorized by displacement and location. Displacement of fracture is defined as a greater than 2 mm separation between the fracture fragments. In the Superion group, 26 of the 31 fractures observed were displaced, and the control group, 15 of the 17 fractures were displaced. And these numbers are similar.

Fracture location. The majority of Superion fractures were coincident with the device: 80% or 25 out of 31 fractures. In the control, there were only five of those coincident with the device. The majority of fractures in the control group were anterior to the device. Twelve out of the 17 fractures, or 70%, were anterior to the device in the control group, and in the Superion group, 4 out of the 31 fractures, or 12.9%, were anterior to the device.

Healing of the spinous fractures were also assessed at 24 months. In the Superion group, 6 out of the 26 fractures, or 23.1%, that were displaced were noted to have healed. In the control, the 6 displaced fractures out of 15 displaced, or 40%, had healed at 24 months. Fractures that were coincident healed at a rate of 28% or 7 out of 25 with the Superion group and 1 out of 5 or 20% in the control group. With the anterior fractures the percentages were similar, with 2 out of the 4 for Superion and 6 out of 12 for control.

The Sponsor provided analysis of the clinical outcome assessments in the study, and the success rates of these outcomes were compared in those subjects with fractures and those without. The outcomes compared were for pain, function, and quality of life. In both arms, the outcomes for the subjects with fractures were comparable to those without fractures in all of these categories. Based on this analysis, the Sponsor concluded that the spinous process fractures were largely asymptomatic and therefore of no clinical significance.

We will be asking the Panel for input on this methodology and the conclusions drawn.

There was a small number of fractures associated with reoperation and revision,

namely, four fractures in the Superion group, or 2.6%, and two in the control group had a reoperation associated with the fracture. The fractures were categorized as adverse events by the clinical events committee. Twenty-two of the fractures, or 11.6%, were determined to be adverse events in the Superion group, and 13 or 6.5% for the control group were determined to be adverse events.

Safety is also assessed by the number of reoperations. At 36 months, a total of 49 reoperations were performed in the Superion arm. The majority of these involved removal of the device. Of these, four of the removals were performed for spinous process fractures.

In the control group there were 44 reoperations, and again, the majority involved removal. Two reoperations occurred due to spinous process fractures. In two instances spinous process fractures occurred intraoperatively, and implantation of the device was aborted.

In summary, the overall adverse event rates between Superion and control arms of the study are similar.

Radiographic observations occur at a similar rate.

Radiographic failure is driven by spinous process fractures in the investigational group and by migrations or dislodgements in the control group.

The incidence of spinous process fractures may be underreported due to the type of imaging used to diagnose these fractures.

Data demonstrating the clinical sequelae of fracture are indeterminate.

Rates of reoperation are similar, and the majority of subsequent procedures involve device removal.

We will be asking the Panel a voting question on whether a reasonable assurance of safety has been demonstrated for this device for its proposed intended use.

In this study, individuals were considered a success if they met all of the following conditions at the 24-month follow-up time point:

1. Clinically significant improvement compared to baseline as determined by meeting two out of three domains of the Zurich Claudication Questionnaire (in other words, improvement in physical function greater than or equal to 0.5 points, improvement in symptom severity by greater than or equal to 0.5 points, a score of less than or equal to 2.5 points on the patient satisfaction domain);
2. The absence of reoperations, removals, revisions, or supplemental fixation at index level;
3. No major implant or procedure-related complications; and
4. No clinically significant confounding treatments.

We will be asking the Panel to comment on the overall success definition and the time point utilized in this clinical trial.

In this study, implant- or procedure-related complications were defined as no dislodgment, migration, or deformation, new or persistent worsened neurological deficit at the index level, spinous process fractures, deep infection, death, or other permanent disability attributed to the device.

Clinically significant confounding treatments were defined as epidural steroid injections or nerve block procedures, spinal cord stimulators, or rhizotomies.

The Superion treatment demonstrated a success rate of 52.7% as compared to 50.2% for the control. The study also met its endpoint of non-inferiority for Superion to control. Although non-inferiority was demonstrated, both Superion and control success rates were below the 65% rate that was expected, and it is not clear how these treatments would compare to the standard of care.

The next two slides show a listing of 24-month results for the components of the primary endpoint. Components 1 and 2 are in this slide and 3 and 4 in the following slide, and each have success rates of at least 80% or higher for both treatment groups.

The ZCQ responder and reoperations components numerically favored the control device, while complications and confounding treatments favored the Superion device.

The secondary clinical endpoints can also be considered in terms of success rates. In general, these endpoints showed 60% to 70% success rates and results were comparable in the two groups. ODI success was defined as greater than a 15-point improvement. Success was 63% for Superion and 67% for control. VAS pain success was defined as 20 mm or more reduction from baseline. Back pain success was 67% for Superion and 68% for control. Worse leg pain VAS success was 76% for Superion and 77% for control. Short Form quality of life success was defined as maintenance or any improvement, and the physical component had a success rate or 81 for Superion and 90 for control. Mental components had success of 60% for Superion and 67% for control.

Patient satisfaction was similar between treatment groups and was above 80%. Eighty-six percent of Superion patients and 88.5% of control patients were satisfied or somewhat satisfied. And 83% of Superion and 84% of control patients would definitely or

probably have the same treatment again.

At 36 months, results showed somewhat more of an advantage for the Superion treatment. Specifically, at the 36-month follow-up, the composite clinical success rate was 53% for Superion and 38% for control. There was a noticeable difference also for worse leg pain VAS. There is missing data and the VAS endpoints have lower follow-up rates. These results could be more biased due to not including this unobserved data. There are numerical advantages for Superion in the ZCQ symptom severity and back pain VAS.

In summary, the overall composite endpoint success rates were similar at 24 months. Superion was 52.7% and control, 50.2%. Similar improvement in neurogenic intermittent claudication symptoms as measured by the Zurich Claudication Questionnaire score at 24 months postoperatively compared to baseline. Similar functional improvement as measured by the improvement in Oswestry Disability Index scores at 24 months postoperatively compared to baseline. And there's similar maintenance or improvement in neurological status at 24 months postoperatively.

We will be asking the Panel a voting question on whether a reasonable assurance of effectiveness has been demonstrated for the PMA device for its proposed intended use.

We'll now be having the statistical review by Dr. Bonangelino.

DR. BONANGELINO: Good morning. My name is Pablo Bonangelino. I was the statistical reviewer for the Superion PMA, and I'll be covering some statistical issues and a little bit more on effectiveness.

So, as has been presented previously, this was a Bayesian adaptive, randomized, patient-blinded, non-inferiority trial, and although the study was formally blinded to

patients, the incision location and pattern was different for the two devices and a blinding assessment at 24 months showed that almost all patients correctly guessed their treatment assignment.

In addition, investigators and the Sponsor were unblinded, which does raise the possibility of operational bias. However, note that the Sponsor reports that only one investigator had disclosable financial interest in the device and the VertiFlex company. This was an investigator who served in the role of consulting medical director for VertiFlex.

So here you can also see the definition of the primary endpoint, which has already been discussed.

This is a partial list of the secondary effectiveness endpoints in the study. They include the individual components of the primary endpoint, testing for superiority in the primary endpoint after demonstrating non-inferiority, the Oswestry Disability Index, or ODI, Visual Analogue Scale, or VAS, for back and leg pain, and the Short Form 12 for health-related quality of life, and a patient satisfaction survey.

Here are the details of the non-inferiority design. The study was testing the null hypothesis that the Superion overall success rate is inferior to that of the control, against the alternative hypothesis that the Superion overall success rate is non-inferior to the control. A delta of 10% was chosen as the non-inferiority margin. The claim of non-inferiority would be accepted if the posterior probability of non-inferiority was larger than 0.958. This posterior probability was calculated using non-informative Beta (1,1) priors for each group. The value 0.958 was selected to control the Type I error of the adaptive design.

Note that, at the design stage, the anticipated success rate of the control treatment

was assumed to be 65%, which was not consistent with later study results.

Here are the analysis populations again. They have already been presented by the Sponsor. However, we note that in our understanding of the data, there were three patients in the study with an anesthesia start time but that did not receive a device, specifically one Superion and two X-STOP patients. According to definition, these patients were counted as failures in the mITT population, which is the primary population for the trial.

It is notable that the IDE study had a Bayesian design. However, prior information was not used in the analysis, as all analysis priors used in the study were non-informative. The study did make use of Bayesian multiple imputation for incomplete or missing primary endpoint data. Note that this approach depends on the assumption that missing or incomplete patients are exchangeable with non-missing patients.

Bayesian methods were also used for two interim analyses for sample size adaptation after 250 and 300 patients had been enrolled. However, the criteria for stopping enrollment were not met, and the study continued to the maximum sample size.

Note also that in addition to the Bayesian analyses, the Sponsor made extensive use of frequentist methods for the secondary and exploratory analyses. Although perhaps unusual, such a combination can be acceptable particularly when, as in this case, the Bayesian analyses use objective Bayesian methods which are qualitatively similar to a frequentist approach.

Here is a slide with the primary endpoint again. I would just note that the posterior probability of non-inferiority is above 0.99 for both the mITT and per-protocol populations,

remembering that the threshold of the probability is higher than 0.958.

As has already been mentioned, the non-inferiority margin was 10 percentage points, and the posterior probability in the mITT group was calculated through Bayesian imputation for the missing data. However, qualitatively similar results are observed when using a frequentist completed approach, which results in success rates of approximately 52% and 50% in the Superion and X-STOP groups respectively.

This is a slide highlighting several subcomponents of special interest. These were the reoperation rate, the rate of device dislodgment or migration, and the spinous process fracture rate. But these have already been extensively discussed, so I will not cover them again here.

This table shows baseline and 24-month mean values for the ZCQ components of the primary endpoint and several secondary endpoints, namely, ODI and leg and back pain VAS. It can be seen that the Superion and X-STOP results are highly comparable. Most notable is worse leg pain VAS, which improved from a mean of 67 to 19.8 for the Superion treatment and from a mean of 68 to 20.3 for the X-STOP.

This second table shows baseline and 24-month median values as opposed to previously mean values for the same endpoints. Again, results between the two treatment groups are highly comparable. In addition, note that the improvement in median worse leg pain VAS appears more dramatic, improving from 74 to 3 for the Superion group and 74 to 7 for the X-STOP. VAS back pain similarly shows greater median improvement compared to the mean values.

Missing data at 24 months consisted of seven patients for Superion and 14 patients

for X-STOP, corresponding to follow-up rates of 97% and 95%, respectively. This slide presents several sensitivity analyses, including last observation carried forward, completers, all missing as failures, all missing as successes, best case, and worst case. Note that all of the analyses resulted in posterior probabilities of non-inferiority notably higher than 0.958, with the exception of the worst-case analysis.

Here is a graphical summary of a tipping point analysis of the missing data carried out by the Sponsor. This type of analysis imputes all possible combinations of successes and failures in the missing data for both groups, in order to find the tipping points for the study conclusion changes. As can be seen by the red plus signs, only a few of the missing data scenarios result in the inability to declare non-inferiority. In addition, the green star in the center of the table represents a scenario assuming the missing data are the same as the observed data in terms of success rates. As this point it is quite far from the tipping point and there are relatively few in all scenarios. The non-inferiority result appears quite robust in the missing data.

In conclusion, the Superion device demonstrated statistical non-inferiority for the primary endpoint of composite clinical success, and the non-inferiority conclusion was robust to the analysis population and to missing data. However, Superion and control overall success rates were both low, being approximately 50%.

Again, we will be asking the Panel a voting question on whether a reasonable assurance of effectiveness has been demonstrated for the PMA device for its proposed intended use.

I will now turn it back over to Dr. Wyatt for a benefit-risk assessment.

DR. WYATT: Good morning. This is Zane Wyatt again.

Just in brief, to recap the FDA's presentation thus far, a summary of the benefits of the device have been identified as improvement in neurogenic intermittent claudication symptoms as measured by the ZCQ score, functional improvement as measured by ODI, maintenance or improvement in neurological; and despite longer operative times, less blood loss was reported during the surgical implantation of the Superion device as compared to the control device, although it should be noted that operative times were slightly longer.

Also, in summary, the summary of the risks of the device identified during the study include an overall rate of adverse events that was comparable to the control device, an overall rate of serious adverse events which was comparable to the control device, and the rate of serious adverse events that were either device or procedure related where the Superion device was comparable to the control device at approximately 21.1% for the Superion device and 23.4% for the control device. It should be noted that these percentages include unknown and undetermined events.

Additionally, the incidence of spinous process fractures observed with the Superion device was numerically higher than those observed for the control device, as reported by the independent radiographic reviewers, and the long-term effect of these fractures on safety and effectiveness of the device is unclear.

It should also be noted that through 24 months there were a total of 38 reoperations or revisions in the Superion group compared with 29 reoperations or revisions in the control group.

At this point the FDA would like to make a brief summary of other selected factors which may impact this benefit-risk ratio.

Firstly, the overall success rate for both the investigational and control cohorts is just over 50% using a composite endpoint which includes clinical success, lack of additional treatment for stenosis, and lack of radiographic observations at 24 months.

To date, randomized controlled trials cited in the FDA's Executive Summary have not shown an advantage for the use of non-fusion interspinous process devices compared to traditional lumbar decompressive surgery in the treatment of lumbar spinal stenosis. In addition, in the same literature references which were previously cited, non-fusion interspinous process devices have been associated with higher reoperation rates compared to traditional lumbar decompressive surgery for treatment of lumbar spinal stenosis at both 1- and 2-year follow-up.

Additionally, although the rate of revision surgery was not statistically different between the Superion group and the control group, literature has shown that interspinous process spacers are associated with higher rates of revision surgery compared to spinal decompression or spinal fusion.

Sensitivity analyses were conducted which supported the conclusions of this study.

The risks may be potentially mitigated by labeling of the device, if the Superion Interspinous Spacer is found approvable.

And it should also be noted that upon approval of this device, if done, post-approval studies will be conducted to study the long-term performance of the device.

The Agency will be asking the Panel a voting question on whether a favorable

benefit-risk has been demonstrated for this PMA device for its proposed intended use.

I would like to now introduce Dr. Ghambaryan, who will review the post-approval study considerations which have been presented by the Sponsor.

DR. GHAMBARYAN: Good morning.

Prior to the presentation of the post-approval study, or PAS, considerations, please be reminded that the discussion of a post-approval study prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.

The plan to conduct a post-approval study does not decrease the threshold of evidence required by FDA for device approval.

The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit-risk balance.

Through the review of the premarket data, the FDA review team has identified postmarket concerns that may need to be addressed if VertiFlex's Superion Interspinous Spacer is approved.

Firstly, in the IDE study, 190 patients completed 24 months follow-up with Superion, which is a third kind of a device. The continuation of the follow-up of the IDE cohort and a new post-approval study may provide longer-term benefit-risk information up to 5 years on Superion.

Also from the pivotal study, we do not have device safety and effectiveness comparisons to decompression, which is a standard surgical treatment option. As was

mentioned before, the compression does not require use of a permanently implantable device. Therefore, FDA believes that it is necessary to evaluate the postmarket device performance with regards to safety and effectiveness as it compares to alternative device-free surgical treatment.

Secondly, the data from the pivotal study demonstrated that the use of the device may be associated with spinous process fractures. Spinous process fractures within the PMA were diagnosed using plain radiographs. However, recent literature referenced in the Executive Summary suggests use of computed tomography, or CT, scans for the accurate diagnosis of the fractures. The use CT scans in a post-approval study may provide an estimation of the incidence of spinous process fractures associated with the device use. Additionally, it may provide information on the clinical relevance of the fractures.

The applicant proposes to conduct two post-approval studies. The first proposed PAS will involve longitudinal prospective evaluation of all IDE patients who were not determined to be failures during IDE stage. Similar to the IDE, the study hypothesis is performance of the Superion is non-inferior to the X-STOP; 136 Superion and 143 X-STOP patients are anticipated to be enrolled in the post-approval study.

The second proposed post-approval study, actual conditions of use, is the new enrollment, randomized clinical trial. The study will evaluate Superion performance within postmarket settings against IDE Superion performance and compare clinical status of patients implanted with the device relative to the surgical decompression alone at 24 and 36 months post-implantation.

This table presents an overview of the applicant's post-approval first proposal for

the extension of the pivotal investigation. As was mentioned before, the purpose of the first study is to continue monitoring safety and effectiveness of the device in the premarket cohort.

The primary endpoint is the composite success of two out three domains of Zurich Claudication Questionnaire, no reoperations, revisions, removals, or supplemental fixation at the index level, and no major implant- or procedure-related complications. The study will continue for an additional 3 years, or 5 years total. The same as the IDE, a Bayesian technique will be used to establish non-inferiority of Superion to the X-STOP. X-rays will be employed to collect radiographic data including information on incidence of spinous process fractures.

The second post-approval study proposed by the applicant is the new enrollment, randomized clinical trial. Study subjects will be randomized in a 1:1 ratio to either Superion or surgical decompression. As proposed by the applicant, the primary objective is to compare Superion performance at 24 months to the pivotal IDE Superion performance. The secondary objectives are to compare clinical status of patients implanted with the Superion device to surgical decompression at 24 and 36 months postoperatively.

Patients with moderate lumbar spinal stenosis at one or two contiguous levels from L1 to L5 will be selected for the participation. The sample size of 150 patients per group, plus 15% to account for the losses to follow-up, is needed for the hypothesis test and for the Objective 1. The primary study hypothesis is the likelihood of PAS Superion patients achieving Month 24 composite success will be non-inferior to the one achieved at 24 months in Superion IDE study patients. Secondary hypothesis is that Superion will be non-

inferior to decompression, in terms of the proportion of patients expected to achieve Month 24 and Month 36 composite success.

The primary endpoint is a composite success criteria identical to the one used in the IDE and described earlier today. Slight modification is made for the Month 36 testing in regards to lumbar injections. Specifically, for Month 36 composite success, only lumbar injections occurring within 12 months of the Month 36 visit will indicate Month 36 composite success failure. The Sponsor is planning to employ x-rays at the start of the study to identify spinous fractures and perform CT scans at 24 months for only symptomatic Superion subjects. The subjects will be followed for 3 years. A Bayesian technique will be used to establish non-inferiority for the Objective 1 and non-inferiority and then, if possible, superiority for the Objectives 2 and 3.

Now I will continue with the FDA assessment of the proposed post-approval study. As mentioned previously, within the current outline of the long-term follow-up of the IDE cohort, CT scans are not proposed to evaluate spinous process fractures in the Superion and X-STOP groups. This may decrease the accuracy in identification of these fractures. FDA believes that in order to accurately evaluate the rate of spinous fractures, CT scans should be utilized as diagnostic method.

In the afternoon, the Panel will be asked to discuss the role of CT scans in evaluating subjects (in both the Superion and X-STOP treatment groups) for spinous process fractures in order to assess long-term safety profile of the Superion device within the long-term follow-up post-approval study.

As mentioned previously, in the proposal of actual condition of use randomized

clinical trial, the primary objective is to demonstrate that Superion performance is not clinically inferior in the new study Superion subjects as compared to the pivotal IDE Superion subjects. The FDA does not believe the primary objective is the most clinically appropriate to address long-term benefit-risk ratio.

In the afternoon, the Panel will be asked to discuss the clinical importance of this objective and discuss the most clinically relevant primary objective of the new enrollment post-approval study.

Additionally, the proposed new randomized clinical trial states that CT scans will be done at 24 months only in symptomatic (identified by plain radiograph) Superion subjects. FDA believes that in order to accurately evaluate the rate of spinous process fractures, CT scans should be used in asymptomatic patients as well.

In the afternoon, the Panel will be asked to discuss the most appropriate time points for CT evaluation to identify spinous process fractures, as well as whether or not there should be different algorithms used in symptomatic and asymptomatic subjects. If different algorithms are recommended, please discuss the specific criteria that should be used to define symptomatic subjects.

This concludes the FDA presentation.

DR. RAO: I would like to thank the FDA speakers for their presentations.

Does anyone on the Panel have brief clarifying questions for the FDA?

Dr. Gilbert.

DR. GILBERT: So, in the presentation of the clinical outcome measurements stratified by presence or absence of spinous process fracture at any time point, 24 months,

the table that you presented that was part of the written report has a denominator for the fractures of 23. And I think this goes to Dr. Rao's earlier comments about what numbers are used in the counting of fractures for the Superion, and I'm wondering if FDA has any comments on that. Shouldn't that be 31?

(Off microphone comment.)

DR. RAO: Could you use the microphone and start again, please?

DR. ADEGBOYEGA-PANOX: Sorry. We do believe that the number 31 should be the denominator, but this is the Sponsor's analysis.

DR. RAO: Dr. Yang.

DR. YANG: So I'm looking at Slide 43, and you were talking about these device removals, and I think there's like six patients, seven patients that had device removal either with another procedure or with device removal. Any of those have spinous process fractures?

DR. ADEGBOYEGA-PANOX: For the control, you mean?

DR. YANG: For -- oh, the control reoperations. Okay. What about for Superion? Sorry.

DR. ADEGBOYEGA-PANOX: For Superion there were four reoperations for spinous --

DR. YANG: There were -- oh, I see. It looks like there were 13, right?

DR. ADEGBOYEGA-PANOX: I'm sorry?

DR. YANG: One slide before. I'm sorry.

DR. ADEGBOYEGA-PANOX: Right.

DR. YANG: Forty-two.

DR. ADEGBOYEGA-PANOX: Yeah. For Superion there were four removals secondary to spinous process fracture.

DR. YANG: So 4 of those 14 did have -- wait, that's two different things. One is how many of those patients that had the device removed did have a spinous process fracture? And I guess the flip side of it is how many of them had the device removed because of the spinous process fracture.

DR. ADEGBOYEGA-PANOX: I know that four patients with spinous process fractures in the Superion group had this device removed. And the answer to the second question is we didn't have that information.

DR. YANG: Okay. And then on Slide --

DR. RAO: Let me just jump in, Dr. Yang, before your second question, because this just follows on that.

I believe one of the slides you presented said that the device was removed maybe in one patient as a result of a spinous process fracture. I'm just wondering --

DR. ADEGBOYEGA-PANOX: No, four.

DR. RAO: There were four patients with spinous process -- who had devices removed, who also had fractures. But I think I saw in one of your slides --

DR. YANG: Yeah, that's what I'm asking.

DR. RAO: -- that there was one device removed because of a spinous process fracture, and I'm just wondering if you had further information on that. Or you can get us information on that after lunch, if you don't mind.

DR. ADEGBOYEGA-PANOX: Okay.

DR. YANG: Thank you, Dr. Rao. I have one follow-up.

DR. RAO: You had a second question, Doctor?

DR. YANG: Yes. So on Slide 30, discharge was 0 to 7 days, which I found a little odd given that this procedure is -- you know, were there any device -- I guess, were there any device removals and fusions in that first 0 to 7 days that made their stay 7 days long?

DR. ADEGBOYEGA-PANOX: No, there were two instances of intraoperative failure -- three instances, one with Superion and two with the control, that they were unable to place a device.

DR. YANG: And so they went on to another surgery?

DR. ADEGBOYEGA-PANOX: Another procedure, yes.

DR. YANG: Which is why the 7 days. Thank you.

DR. RAO: Dr. Lyman.

DR. LYMAN: I had a question about the imputation of outcomes. There was a few slides around that, and it looks like the -- I guess my primary question is, were the outcome scores imputed, and if so, were they the complete scores that were imputed or were they individual items from those surveys that were incomplete?

DR. BONANGELINO: I'd have to get back to you on how exactly that was done. Basically, the completers were used to -- the distribution for the completers were used to impute the incomplete subjects, and I'd have to get back to you afterwards for more detail.

DR. LYMAN: Okay, I have a follow-up on that, then, because the best I can tell, about 65% of the entire cohort for both groups actually completed their 2-year outcome surveys. Now, that's just me trying to cobble together from the different tables that were presented.

So that would suggest either those who were considered failures in other ways weren't asked for 2-year outcome surveys or we have quite a bit of missing data that may have had to have been imputed to get to those levels. I'm just trying to get clarification around that.

DR. BONANGELINO: What happened was, there was terminal failures that were counted as failures, so therefore it was not counted as missing data.

DR. LYMAN: I see. Okay.

DR. BONANGELINO: Yeah.

DR. LYMAN: So then, I guess I just want clarification around how frequently imputation was used for the outcome scores and then what imputation. What was being imputed exactly?

DR. BONANGELINO: There was imputation of the seven Superion and 14 X-STOP patients who didn't have primary outcome data.

DR. LYMAN: So those patients had no outcome data, okay.

DR. BONANGELINO: They did not have a determination of outcome success or failure at 24 months.

DR. LYMAN: Okay, thank you.

DR. BONANGELINO: Sure.

DR. RAO: Dr. Graf.

DR. GRAF: One question I have is regarding the post-approval study consideration for the Study No. 1, where it's being proposed that the use of CT scans is performed. Has the FDA taken into consideration the significance of performing multiple CT scans for diagnostic purposes on these subjects? That should be taken into consideration.

DR. ADEGBOYEGA-PANOX: I think we're actually asking for the Panel's input on that particular question.

DR. RAO: I have a couple of questions here. I guess this could go either to Dr. Wyatt or Dr. Panox.

Your secondary endpoints listed in the material that was sent to me prior to the meeting, and the printed material, lists one of the secondary endpoints is to evaluate maintenance of distraction defined by less than 4 mm of measurable decrease in posterior disc height on successive radiographs at 6 months -- 6 weeks and 24 months. But I didn't hear anything about that from the Sponsor's presentation earlier today. And, in fact, in their presentation there's a discrepancy where they said they excluded maintenance of distraction. Can you explain this discrepancy? Why does yours say it should be one of the secondary endpoints and theirs doesn't?

DR. ADEGBOYEGA-PANOX: I can't really explain the discrepancy. They have submitted data about maintenance of distraction at 24 months. We do have that data.

DR. RAO: Would you be able -- I mean, I asked the Sponsor the same question this morning. So, between the two of you, I hope that we'll have some information on maintenance of distraction at 24 months.

DR. ADEGBOYEGA-PANOX: Yes.

DR. RAO: I have another question for Dr. Bonangelino. Dr. Bonangelino, I think my question may be somewhat similar to Dr. Lyman's, but it's in plain English and not in statistical language.

(Laughter.)

DR. RAO: But you mentioned that the success rate that was assumed prior to the study at the beginning during the design phase was 65%.

DR. BONANGELINO: Correct.

DR. RAO: Then you had a success rate of about 50% to 52%, in that range --

DR. BONANGELINO: Um-hum.

DR. RAO: -- meeting the success endpoints, the composite success endpoints. Did you do any studies to see, with the lowered clinical success rate, what should the probability of non-inferiority be? And was that met with the lowered success rates?

DR. BONANGELINO: As I understand that, there's the issue of the non-inferiority margin, which is quite standard for spinal studies to be 10%, and that usually doesn't vary with the actual observed success rate.

DR. RAO: Maybe I asked the question wrong. Maybe it's not the 10% I'm referring to, but the 0.9958.

DR. BONANGELINO: Oh, the 0.958.

DR. RAO: Yeah, the 0.9958. Should that be different with a lowered success rate?

DR. BONANGELINO: No.

DR. RAO: And was that met with the data available?

DR. BONANGELINO: No, the 0.958 was chosen -- well, the standard value that corresponds to an alpha of 0.05 in the usual testing is 95%, and this was increased 0.958 because of the adaptive nature of the trial and not because of the estimates of the success rates. The fact that the trial was adaptive made it necessary to raise the threshold somewhat to control the overall level of the Type I error. And that was verified with

simulations, which I'm quite sure the simulations included scenarios where the success rates were lower and so forth.

But I think the other issue that that raises, the success rates raises, is the issue of whether the treatment would have been superior to non-operative care. In other words, because the success rates were lower, you're demonstrating non-inferiority to something that's a lower success rate. Would that still be better than a rate that you would have observed with another treatment, that you should be superior to another treatment? So that's the other issue with the lower success rates.

But from what I understand, in the X-STOP IDE study there was -- a success rate of non-operative care was very low. And granted, it was an open-label study, but it was 4.9%, something like that, or 5%. So even though the non-inferiority is lower compared to non-operative care, there would still be the possibility of -- the other issue is whether demonstrating that it's still superior to no treatment essentially. In other words, the control was effective enough to be superior to no treatment. So I hope that answers your question.

DR. RAO: Are you generally satisfied that the statistical criteria for non-inferiority were met with the data as used?

DR. BONANGELINO: Yes, I'm quite certain that non-inferiority was met with the definitions that were given. Yeah. I mean the point estimate is somewhat above the control, and I think that's why the posterior probabilities were quite a bit higher than 0.958. But I think it's a clinical question as to whether the success rates are high enough to justify the risks, and I guess that's why we're here.

DR. RAO: Dr. Golish.

DR. GOLISH: I appreciate your preciseness in saying, I'm clear that non-inferiority was met with the definitions used, the definitions used including the arbitrary non-inferiority margin of 10%, which instead of being chosen from a well-designed and well-conducted superiority trial based on the effect size is instead chosen without any better criteria to be 10% because it's conventional. But you'll admit that a wrong choice of that number can result in a situation where you have non-inferiority relative to the control, but you do not have superiority relative to sham. Agreed?

Then the IDE trial for X-STOP was, in fact, not relative to sham, relative to usual care -- as you put it, no care -- worsening that problem further. So, and the imposition of these arbitrary parameters in your definition, as you very well put it, mitigates that statement quite substantially.

DR. BONANGELINO: Yes, thank you.

DR. RAO: One more question here. This is again based on your previously submitted printed material to us. In the printed material, I just need some clarification in the differences between Table 9 and Table 10. In Table 9, you mention the leg pain incidence between the investigational and the control group as 20% and 23%, respectively. But in Table 10, you say device-related adverse events, leg pain, was one. Twenty and 23% in Table 9, but in the device-related adverse events, Table 10, you say it's one patient with leg pain, and I'm just wondering if you could clarify the discrepancy between the 20% with leg pain in Table 9 and the one patient with leg pain in Table 10. If you could do that after lunch, that would be great.

Dr. Trier.

DR. TRIER: Yes, this is Dr. Trier.

And, again, I would like to offer a comment with regards to Dr. Golish's last comment. You know, one of the merits of being able to look at studies over time is that, while things may not be as precise and they seem to be numbers pulled out of the air, there is a merit to looking at what is typically used in standards for the delta. And so, for example, when you look at studies that have been conducted and used for PMAs in the past, they were because of standards across the industry and across the interactions with FDA. And a delta of 10, it's my understanding, for studies of this type is a well-respected and accepted standard for deltas. So I guess I wouldn't see it as being quite as capricious as what it may seem, but that it is certainly a recognized standard.

DR. RAO: Thank you, Dr. Trier.

Dr. Gilbert.

DR. GILBERT: So, as I understand it, one of the questions we're going to be asked to discuss later is altering the post-implantation imaging of the patient to identify spinous fracture. So I'm just wondering, if we were to adopt some different -- or propose, recommend some different rate of imaging of the patients, do you think that will affect the clinical care, what the doctor does with the patient, if they identify fracture at 2 days or 1 week or 2 weeks post-surgery?

DR. ADEGBOYEGA-PANOX: One of the things that's not 100% clear is whether or not in fact these spinous process fractures have no clinical consequence. We do know that this device relies on the integrity of the spinous process to set its treatment effect, and we're

not 100% clear that this treatment effect is not lost or is maintained based on the data that we have received.

So your question is, are we going to change -- is the surgeon going to change his treatment if he finds more spinous process fractures? And I believe that surgeons, when they discover an abnormality on x-ray, their next step is to evaluate the patient as to whether there are any symptoms related to that finding and act on that.

DR. GILBERT: And just to follow up. The assessment of success clinically was at 24 months, and the preponderance of fractures occurred --

DR. ADEGBOYEGA-PANOX: Right.

DR. GILBERT: -- before 6 weeks. So I think Dr. Lyman pointed that out earlier.

DR. ADEGBOYEGA-PANOX: Yes.

DR. GILBERT: So there's a large time difference between the two events.

DR. ADEGBOYEGA-PANOX: That's correct. The other thing, too, is that two-thirds of those fractures had not healed at 24 months, and we were thinking that non-healed fractures at 24 months were more a concern.

DR. RAO: Mr. O'Brien.

MR. O'BRIEN: I just have a patient and a common question. On the tables that refer to success, the 80% success rate that's reported, it indicates 152 patients were "success." But then on the follow-up proposals or the postmarket proposals, it starts out with 136 as being the non-failed patients. What is the difference between the 152 and the 136? How did we get down to 136? I thought we said there was 152 success.

DR. BONANGELINO: Are you referring --

MR. O'BRIEN: The applicant's proposal for the postmarket study indicates that the sample size will start out with the 136 non-failed patients, and I'm just trying to reconcile that with the previous tables that indicate that the success patients were 152. How did we get from 152 to 136? I can't follow that. I don't know where those patients went.

DR. BONANGELINO: I think we'll have to get back to you.

MR. O'BRIEN: Okay, fine.

DR. RAO: I have another question, but before that, there were two members of the public that asked to speak at this hearing. If they're around, please raise your hands and then we might change the schedule just a little bit and go before lunch with the two of you. So please get your thoughts organized and I'll get in touch with you in just a moment.

My other question is again for you, Dr. Bonangelino. You know, it's quite clear -- it appears to me that the margin of difference between the two groups is not that substantial, and a little bit here or there could skew the results. Did you look at whether if you changed the number of fractures, which is considered a failure in the radiographic outcome measures, if you looked at the number of fractures and changed that from the number of non-healed fractures, which I believe the Sponsor is currently using at 21, and bumped that up to 31 fractures, which is the total number of fractures, whether that would tip this over into the not clinically non-inferior -- not statistically non-inferior group?

And, too, the second part of that question is there were a number of spinous process fractures which I believe were excluded from consideration because they were felt to be at the tip of the spinous process. Now, if we were to assume that the spinous process fracture is not such a big deal clinically but rather represents a settling of the motion segment, and if

that tip of the spinous process fracture is also an indication of some biomechanical settling at the level the device was implanted, then that may also become maybe not clinically relevant but radiographically somewhat indicative of how the implant continues to function.

So did you have numbers of fractures at the tip that were excluded from consideration? And, too, if you threw those into the equation, does it tip one way or the other? And, too, if you use 31 instead of 21, does it tip one way or the other? And you may not have answers to that right now, but it would be great if you could give us some clarification on that after lunch.

DR. BONANGELINO: Okay, we will. Yeah.

DR. RAO: Any other questions from the Panel?

(No response.)

DR. RAO: Good. Well, it's almost 11:30. We're a little bit ahead of schedule, so we're going to go ahead with the Open Public Hearing session. It is now 11:30. I'd like to -- let me see where we are on this.

We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Lieutenant Commander Anderson will now read the Open Public Hearing disclosure process statement.

LCDR ANDERSON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such

transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. RAO: For the record, we have received two requests to speak for today's meeting. Each scheduled speaker will be given 5 to 10 minutes to address this Panel. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates that each speaker remain cognizant of their speaking time.

The first speaker is Christina Silcox, Senior Fellow at the National Center for Health Research, formerly known as the National Research Center for Women and Families.

Ms. Silcox.

DR. SILCOX: Thank you for the opportunity to speak today. I'm Dr. Christina Silcox. I have a Ph.D. in medical engineering and medical physics from MIT, and I am a senior fellow at the National Center for Health Research. Our research center scrutinizes scientific and

medical data and provides objective health information to patients, providers, and policymakers. These are the perspectives I bring with me today. We do not accept funding from device companies, and therefore I have no conflicts of interest.

Lumbar spinal stenosis is one of the most common indications for spine surgery in patients older than 65, and its prevalence in the United States is expected to rise almost 60% by the year 2025. This means the FDA's decision about whether or not to approve this device will affect the lives and health of many men and women.

The Superion IDE trial showed that the Superion ISS device is non-inferior to the X-STOP device, but does that mean it should be approved? We have two major concerns. First, we agree with the FDA's scientists that the 16.3 spinous fracture rate is likely to have clinical significance despite the Sponsor's claim that it doesn't. We base that on the fact that the hypothesized mechanism of action depends on intact spinal processes. The Sponsor's Executive Summary itself states that part of the purpose of the IDE was to validate the device's mechanism of action. We are concerned that the similar successful clinical outcomes for patients with and without spinous process fractures means that the mechanism of action is not understood.

Is it possible that the adjacent soft tissue and musculature is playing more of a role than previously thought? If so, what is the potential long-term effects? Sixty-eight percent of the Superion fractures were unhealed at 24 months compared to 59% for the X-STOP. Is the device placement preventing healing? What are the long-term potential effects, if so?

This is a device that has been proposed for use in patients as young as 45 years old. It is essential to understand the mechanism of action in order to understand the long-term

effects of this permanent implant and to avoid the risks of revision surgery in the future.

Our second concern is the effectiveness data. The Committee is being asked whether this product should be approved based on its demonstrated non-inferiority to the X-STOP device. However, the FDA's Advisory Committee recommended against approval of the X-STOP device because of its questionable benefits. That Advisory Committee thought that the data from the pivotal trial did not demonstrate that the benefits outweigh the risks. The FDA approved the device anyway, and since that time, real-world evidence has clearly shown that the X-STOP is even less beneficial than the pivotal study indicated. In the study presented today, successful outcomes were only found in approximately 50% of patients in both arms, and more than 25% of the Superion patients had to have revision surgery by 3 years.

It is common for studies submitted to the FDA to have more favorable outcomes than surgical devices will have in the real world. That's because the surgeons are the best that the Sponsor can identify and the patients are carefully selected according to a protocol that is unlikely to be followed in the real world. For that reason, we can expect that in the real world, the Superion ISS device will be even less beneficial than it was in the study by the Sponsor, probably not as good as the X-STOP, and therefore less good than the surgery with either the X-STOP or Superion ISS. Given that the Superion found a correlation between the spinous process fracture risk and the spinous process placement of the device during surgery, this is a particular concern.

I do not know why the FDA ignored the previous Advisory Panel recommendation and approved the X-STOP anyway. But I do know that in 2004 the FDA had lower standards

for PMA approval than they have today. The FDA leadership has changed and efforts have been made to be more consistent. If you consider the higher standards of evidence currently used for this very important indication and the real-world data indicating that the X-STOP device has risks that outweigh its benefits for most patients -- if you were considering the X-STOP today, it is very likely that this Advisory Committee would again recommend against approval and this time the FDA would agree.

However, the task today is to focus on the Superion and whether its benefits outweigh the risks of surgery without the device. It does not make sense to approve another device meant for the same population that does not demonstrate superiority even when the best surgeons and most appropriate patients are selected for the study.

Even more importantly, when the X-STOP was approved 11 years ago, it filled a gap between open surgery and nonsurgical treatments that were not very effective. Since then, minimally invasive surgery techniques have become much more common.

In summary, the mechanism of action is not clear, making the long-term benefits and risks unknown. This device is no better than the X-STOP and inferior to surgery without the device, even under the ideal circumstances of a clinical trial. It is likely to be even less beneficial in the real world. Finally, the X-STOP is approved because it filled a need for patients who could not undergo open surgery. That need has been met because other more effective minimally invasive surgeries have been developed.

We urge you to vote no because the data are insufficient to prove that the benefits outweigh the risks or a reasonable assurance of safety and effectiveness.

Thank you.

DR. RAO: Thank you, Dr. Silcox.

We did receive one additional request to speak after the *Federal Register* deadline. This presenter will be given 5 minutes. I call upon Dr. Kathryn Simpson, Manager of Clinical and Regulatory Affairs, the Orthopedic Surgical Manufacturers Association, or OSMA.

DR. SIMPSON: Good morning. My name is Kathryn Simpson, and I'm the director of regulatory affairs at Medtronic. I do not have any affiliation or financial interest in the device being presented here today. I speak here today on behalf of the Orthopedic Surgical Manufacturers Association, or OSMA.

OSMA, a trade association with approximately 30 member companies, welcomes this opportunity to provide general comments at today's meeting of the Orthopaedic and Rehabilitation Devices Panel. OSMA's comments should not be taken as an endorsement of the product being discussed today. We ask instead that our comments be considered during today's Panel deliberations. These comments represent the careful compilation of the member companies' views.

OSMA was formed over 50 years ago and has worked cooperatively with the FDA, the American Academy of Orthopaedic Surgeons, the American Society for Testing and Materials, and other professional and medical societies and standards development bodies. This collaboration has helped to ensure that orthopedic medical products are safe, of uniform high quality, and supplied in quantities sufficient to meet national needs. Association membership currently produces over 85% of all orthopedic implants intended for clinical use in the United States.

Like the American public, OSMA has a strong invested interest in ensuring the

ongoing availability of safe and effective orthopedic devices. The deliberations of the Panel today and the Panel's recommendation to FDA will have a direct bearing on the availability of new products designed to improve the quality of life of patients treated in the United States. We urge the Panel to focus its deliberations on the product's safety and effectiveness based on the data provided.

The FDA is responsible for protecting the American public from drugs, devices, food, and cosmetics that are either adulterated or are unsafe and ineffective. However, FDA has another role, to foster innovation. The Orthopedic Devices Branch is fortunate to have available a staff of qualified reviewers, including a board certified orthopedic surgeon, to evaluate the types of applications brought before this Panel.

The role of this Panel is also very important to the analysis of the data in the manufacturer's application and to determine the availability of new and innovative products to treat patients in the United States. Those of you on the Panel have been selected based on your expertise and training. You also bring the view of practicing clinicians who treat patients with commercially available products.

Our objective here today is to emphasize two points that will have a bearing on today's deliberations:

1. Reasonable assurance of safety and effectiveness; and
2. Valid scientific evidence.

Point 1: Reasonable assurance of safety and effectiveness. There is reasonable assurance that a device is safe when it can be determined that the probable benefits to health outweigh the probable risks. Some important considerations associated with this

standard include valid scientific evidence and proper labeling and that safety data may be generated in the laboratory, in animals, or in humans.

There is a reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that the device provides a clinically significant result in a significant portion of the target population. Labeling in the form of adequate directions for use and warnings against unsafe use play an important role in this determination.

Point 2: Valid scientific evidence. Valid scientific evidence consists not only of well-controlled investigation, but also partially controlled studies, studies in objective trials without matched controls, well-documented case histories, and reports of significant human experience with a marketed device. While a well-controlled investigation may be the highest order of evidence used to determine safety and effectiveness, OSMA respectfully reminds the Panel that other types of valid scientific evidence may provide a reasonable assurance of safety and effectiveness.

In addition, while the scientific community recognizes that among the essentials of a well-controlled investigation are the methods of selecting subjects, observing and recording of results as well as a comparison of results and treatment with a control, including a historical control, OSMA also urges the Panel to recognize that a clinical study with some, but not all, of these essentials may yet be a higher order of valid scientific evidence than other types of evidence which can provide a reasonable assurance of safety and effectiveness.

The Panel has an important job today. You must listen to the data presented by the Sponsor, evaluate the FDA presentations, and express an opinion about the safety and

effectiveness of the Sponsor's product. We speak for many applicants when we ask for your careful consideration. Please keep in mind that the standard is a reasonable assurance, balancing the benefits with the risks. A greater degree of certainty is not required.

When considering making recommendations for further studies, remember that FDA takes these recommendations seriously, often as the consensus of the Panel as a whole, and recommendations for additional studies may delay the introduction of a useful product or result in burdensome and expensive additional data collection. Therefore, you play an important role in reducing the burden of bringing to market new products which you and your colleagues use in treating patients. Please be thoughtful in weighing the evidence. Remember that the standard is a reasonable assurance of safety and effectiveness and that there is a broad range of valid scientific evidence to support that determination.

OSMA thanks the FDA and the Panel for the opportunity to speak today. Our association trusts that its comments are taken in the spirit offered, to help the FDA decide whether to make a new product available for use in the U.S. marketplace. OSMA members are present in the audience and are available to answer questions anytime during the deliberations today.

Thank you.

DR. RAO: Thank you, Dr. Simpson.

Does anyone in the audience wish to address the Panel at this time? If so, please come forward to the podium, state your name, affiliation, and indicate your financial interests. You will be given 3 minutes to address the Panel.

(No response.)

DR. RAO: Seeing none, at this time are there any questions from the Panel for the open public speakers?

(No response.)

DR. RAO: If there are no questions from the Panel for the public speakers, I now pronounce the Open Public Hearing to be officially closed. We will reopen again at 1:00 p.m. in case there any walking in at that time.

I think we'll close now for lunch. I'm told that lunch is only available at noon, but you're welcome to make your way there or check out or whatever you have to do. I think we can meet back again at 12:45. Let's meet at 12:45 instead of 1:00. So let's meet at 12:45 after lunch, and we'll resume again.

Thank you very much.

(Whereupon, at 11:45 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:47 p.m.)

DR. RAO: Well, I think the Panel is seated, and I think we have the Sponsor here. Do we have the FDA presenters? We have the FDA presenters here. I think we can get started.

It's almost 1 o'clock, and I just want to open it up to the public one more time. We did that earlier, but just to be fair, is there anyone in the audience that wishes to address the Panel at this time? If so, please come forward to the podium, state your name, affiliation, and indicate your financial interests. You will be given 3 minutes to address the Panel.

(No response.)

DR. RAO: Seeing that there is no one in the audience, we will move forward. We now go on to the Panel deliberations section of our meeting.

As a reminder, although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time, Sponsors and FDA presenters. This helps the transcriptionist identify the speakers.

Is the Sponsor, at this stage, prepared to respond to the Panel's questions posed this morning? And I hope the FDA is prepared to respond to the Panel's questions posed this morning. So let's go ahead and start with the FDA response to the Panel's questions from this morning.

DR. WYATT: Good morning, this is Zane Wyatt, reviewer with the FDA.

So the first issue that the Sponsor -- or sorry, that the Panel had brought up was the

reoperation rate due to fractures, is our understanding. And so according to our understanding of the data which was provided to us, there were four revisions and/or reops which were directly due to a spinous process fracture. We apologize if there is a discrepancy in our reference to one patient. Please note, though, that we defer to the Sponsor if this information is incorrect.

In regards to maintenance of distraction, we did not review any data related to the Sponsor's proposed secondary endpoint of maintenance of distraction because this was not included in the primary endpoint analysis. We therefore defer to the Sponsor to present any analysis they may have conducted on this regard.

In regard to the discrepancy between leg pain in Table 9 and Table 10 of the Executive Summary, Table 9 presents all events, whereas Table 10 presents adverse events which were adjudicated to be device related. So that's the difference between 20% versus one patient.

In regards to the 151 versus 136 patients, the 136 number was at the time the data which was provided to the FDA. When this PMA was initially reviewed, the Agency assumed that all provided patients which had reached their 36-month follow-up visit would be available for postmarket evaluation. At that time, this patient number was 136 patients. As the Sponsor has previously described, it appears that all 151 success patients have now reached their 36-month follow-up visit, so these numbers would coincide.

In regards to if all 31 fractures were counted as study failures, is non-inferiority still maintained, the answer to that question is yes. If we count all tip avulsions and other fractures as fractures, is non-inferiority still maintained? We did not perform that analysis,

so we defer that to the Sponsor.

And as it has been mentioned previously, 10% is the customary non-inferiority margin the FDA has historically accepted for orthopedic clinical trials. It serves our purposes in trials of this type in establishing a reasonable assurance of safety and effectiveness. We do not typically accept adaptive non-inferiority margins as this affects the Type I error.

Thank you.

DR. RAO: Before you leave, Dr. Wyatt, could you just repeat your Point No. 2, the one after the four patients revised due to fracture?

DR. WYATT: Okay. So, if we, in addition, count the four or five, depending on what numbers you use, tip avulsions which were considered fractures, we did not do an analysis of non-inferiority is not -- is still maintained in that regard, and we defer to the Sponsor to address that point.

DR. RAO: A couple of points before that. I think it was the second overall issue that you were talking about. The first issue was there were four patients who underwent revision due to the fracture.

DR. WYATT: Correct.

DR. RAO: And what did you say immediately after that?

DR. WYATT: Okay. We apologize if there was a discrepancy in Dr. Panox's reference to one patient. We note that if there's an incorrect -- if the number four is incorrect, that we defer to the Sponsor in that regard.

DR. RAO: And what did you say after that?

DR. WYATT: Then we moved on to maintenance of distraction. We did not conduct that analysis.

DR. RAO: And why didn't you conduct that analysis? You didn't have the data or you had the data?

DR. WYATT: The data was provided, but it did not affect our primary endpoint analysis, and so therefore we didn't review it.

DR. RAO: Thank you.

Dr. Yang.

DR. YANG: May I ask a follow-up question? So, in those four patients with the spinous process fractures, or five, however you want to count it, given that usually in my practice, spinous process fractures don't really give rise to symptomatology, what was the indication for removal?

DR. WYATT: It wasn't clear from the table which was provided, but it appeared that it would be pain, from the corresponding tables.

DR. YANG: Thank you.

DR. RAO: Are there any other questions for the FDA responses -- based on the FDA responses?

Dr. Lyman.

DR. LYMAN: I just wanted to make a clarification on the non-inferiority and the power which we discussed earlier. Is this an appropriate time to do that?

DR. RAO: This would be fine.

DR. LYMAN: It came up during the FDA.

DR. WYATT: Sure. And I may have to defer to Dr. Bonangelino.

DR. LYMAN: No problem. You said that you don't normally accept adaptive trials and et cetera. But a 10% non-inferiority for an assumed 65% success rate would be 6.5% difference between the treatment groups, and you actually found about a 50, 52% success rate, so that would be a 5.2% difference between treatment effectiveness. Now, you found much smaller than that, but I just think the FDA needs to be aware of what that effect would have on sample size and power in this context. I just wanted to make that comment. I don't think there needs to be a response right now.

DR. WYATT: Okay, thank you.

DR. RAO: Thank you very much, Dr. Wyatt.

I will now call upon the Sponsor to please come up to the podium and introduce yourself and provide responses to the issues that the Panel raised this morning.

MR. STIEGMAN: This is Glenn Stiegman.

There are going to be several speakers -- and they'll identify themselves -- covering a number of different topics, one regarding the question about the control from Dr. Golish. There was also a question about the minimally clinical difference and its validation. Further, another question regarding additional procedures, supplemental procedures that are listed in the Executive Summary; also a clarification between two discrepancies on a slide, from Dr. Graf, the fracture analysis of onset, when that happened and the resulting pain and function; also looking at posterior disc height in fracture and non-fracture patients, as well as the secondary endpoint of distraction.

As the FDA has answered already, the reop causality directly attributed to fracture is

indeed four and one patient in the Superion and X-STOP group.

And with no further ado, I'll invite Dr. Fred Geisler up to talk about the control.

DR. GEISLER: Thank you. Good afternoon. I'm Fred Geisler, a neurosurgeon. I served as chairman throughout the entirety of this study, on the CEC, starting in 2009. I was compensated for my time as being chairman and also as a consultant for VertiFlex. I'm going to be discussing the X-STOP as far as a valid control and what's known about that.

Whenever you do a study, you have to go on the past data and try and build your study so that it's better than prior studies. The X-STOP study was the first study in the field of interspinous spacers. There was a discussion that ensued after the X-STOP study, and both the coflex and the Superion study were based off of these discussions to make superior studies.

If we look at the data trying to compare our current Superion study with the X-STOP control group, which is the first two lines, with the X-STOP IDE data which we have available, which is published, first of all we have to use a slightly different measure than we used in presenting our data. The ZCQ success, we have to combine all three. In our study we used two as per protocol, and the reason for switching to that is that in the X-STOP IDE they only reported all three components for a comparison. The X-STOP, on the bottom part of the slide there, presented their data in three ways, either all, indicated population, or indicated population excluding the inventor study site. Their success score is for 47, 56, and 42%, respectively. The X-STOP, in a comparable measure in the current study, was 64% or superior. I would put forth that the best data on the X-STOP is actually from the study we are talking about today.

The next slide. One of the things we need to defend against is that this was a valid control, and the control is not placebo or sham. Let us just look at the data. If we look at the primary endpoints in the ZCQ, which have already been projected, we notice that all of them in both groups, the Superion and the X-STOP, fall abruptly with a surgical procedure and then persist for 3 years. Although surgery is known to be a powerful placebo, it seems very unlikely that this placebo effect would last for 3 years. And I'm not sure of a reference for placebo effect that long.

If I could have the next slide. If we look at the secondary variables, where we look at the VAS and the worse leg, again, there's a precipitous drop in both groups and then these persist out for the 3-year period. And these changes are clinically significant.

The next slide. If we look at the further secondary variables of the Oswestry Disability Index and the VAS with the back pain, we again notice the abrupt drop with the surgical event and the clinical effect, which is clinically significant to the patient, persists for a 3-year period.

So I would like to put forth that it is our opinion that there was a clinical effect which was measured in the study and in the placebo group, which was shown not only in the primary variable but every secondary variable persisted for 3 years, and that the data in our study is actually the best data for the X-STOP to use as a comparison.

Thank you for your time.

MR. STIEGMAN: Glenn Stiegman again.

One point of note that I forgot to mention. We'll certainly be addressing the mechanism of action in the presence of a fracture as well as the contact area that was

asked earlier.

One point of note. It was asked early on about the minimal clinical difference and whether it was validated as 0.5. The Tully article in *Spine* (2006) does do this in the population that was studied. I just want to make that clarification. I didn't know if that was fully answered when I gave my answer earlier.

Now I'm going to ask Dr. Nunley to come up and talk about the additional procedures or supplemental procedures that were asked earlier on, as well as a clarification point between two slides.

DR. NUNLEY: Hello. Pierce Nunley.

One of the questions that the FDA has brought up is about additional procedures. And again to reiterate what we've presented before, in Superion there were 11 levels in 9 subjects. To dig down into that, two subjects were skin incisions that were extended to facilitate the cannula, six subjects were using the interspinous reamer to prepare that interspinous process space, and one subject did use a Kerrison to shave the hypertrophy tip of the spinous process in order to insert the device.

In the X-STOP there were 16 levels in 12 subjects. Seven subjects had removal of soft tissue in the interspinous ligament just to facilitate the device implantation. Four subjects had resection of the dorsal aspect of the facets, in hypertrophy facets, to facilitate the implant positioning. One subject did have a resection of the ligamentum flavum. And it is important to note that that subject was excluded as that was deemed to be a decompression and a violation of the protocol and is not -- that subject is not part of the data analysis. All 9 Superion and 11 of the 12 X-STOP procedures were

non-decompressive in nature, which I think begs to the question at hand.

So when we look at doing a decompressive procedure, the areas that we're concerned about are the neural foramen and the subarticular region. In the interspinous region when we're removing the interspinous ligament, that cannot be considered a decompressive procedure for the neural elements.

And we actually presented this at the 100-day. This is one of my patients where the left side shows a sagittal foraminal view at L4-5, and the orange arrow shows the exiting L4 nerve root at that level and the stenosis present. And the green circle is actually the hypertrophy of that facet, which is seen in the axial image on the right, where the -- again, the orange arrow is pointing to the subarticular region, which would be the passing L5 nerve root, and the green circle would be that hypertrophied facet joint, which at the -- to place an X-STOP and get it to be sufficiently deep enough would require some debulking of that facet joint. But even if we removed all that was in the green arrow zone, that is nowhere near any area that would be considered decompressive in nature to decompress any of the neural elements. So I want to make sure that we're clear on what those removed.

So the facet debulking and to the osteophyte removal and six patients in the soft tissue removal we do not believe has any effect on actually decompressing any of the neural elements.

I'd like to go on now and try to clarify what I think was maybe a misunderstanding, but this idea of what happens when the device does not work. So, again, I think we need to point out that 80% of the patients ended up having the device and having success with it,

with a less invasive, less morbid procedure. However, for those patients that fail the device, the point that I was trying to make is that the surgery now to fix that problem, the revision surgery, if you will, is kind of like a primary surgery. Yes, the patient had an anesthesia, so there's some risk with that. But the decompressive part of the procedure now is a virgin decompression, which as a spine surgeon is a very different situation than if the antithesis were true and a patient fails a direct decompression, which the failure rates are similar if not greater, that that revision surgery and as a spine surgeon carries with it a greater risk for the patient and decreased outcomes. As we know, a secondary procedure does not typically do as well as a primary procedure.

So I hope that answers the question that Dr. Graf asked, but I wasn't really trying to compare the two. But there is a decision-making difference, as a caregiver, in those two.

Thank you for your time.

DR. BLUMENTHAL: Thank you. Scott Blumenthal. And I'm going to answer the question and further clarify the clinical effect of the fractures.

So this was the slide that you've seen previously, which is the time course of the spinous process fractures, and I won't belabor that. But this is what you're looking at in terms of the different outcomes of patients with and without fractures. And the outcomes, as mentioned, were similar as well.

What these next couple slides show is the time course. The question asked was how did they do at each time point, since the majority of the fractures occurred acutely? And you can see this in the ZCQ, Superion with and without fracture. There was no clinically significant outcome difference at any of the time points or follow-up time periods in the

study.

This is the ZCQ symptom severity, again no significant difference at the individual time points, particularly early when most of these fractures occurred.

VAS back pain, again no statistically significant difference in the Superion arm.

In the X-STOP, this shows the ZCQ time periods; no spike early. No spike early in the symptom severity as well.

And, finally, the only statistically significant difference was in the X-STOP cohort at the 3-month follow-up in patients with and without fracture. They did have a difference in their VAS back pain, and that was statistically significant.

Thank you.

MR. STIEGMAN: Glenn Stiegman again.

So there was a question about posterior disc height in the presence of a fracture versus non-fracture, as well as distraction for the secondary endpoint. The table up here shows that there was no difference between posterior disc height between a fracture patient and a non-fracture spinous process.

Also, as far as the distraction, we don't have a nice table developed. But as far as the distraction as a secondary endpoint, there was no difference between fracture patients and non-fracture patients when showing maintenance of distraction. In fact, both groups were 100%; everyone maintained distraction by the definition in the secondary endpoint.

One point of clarification that was asked about the number of fractures presented in an FDA table, should it be 23 or it should it be 31, all analyses were done on 31 fracture patients. The 23 comes from those patients that were terminal failures, meaning that they

had an epidural injection, a revision, or missing data. So that's why you get 23. There were only 23 available patients out of the 31.

And then, lastly, I'll ask Lisa Ferrara to discuss the mechanism of action.

DR. FERRARA: Thank you. I'm Lisa Ferrara, and I am an independent consultant. My travel and time is being reimbursed by VertiFlex. I'm going to discuss the mechanism of action of the Superion in the presence of a spinous process fracture.

As shown in this data for the Superion, the clinical data shows a decrease in the clinical range of motion for the intact spinous process as well as the fractured spinous process. The decrease in range of motion is consistent to the intact spinous process with the in vitro biomechanical data for the Superion.

The clinical data demonstrated that the Superion continued to block extension in the presence of a spinous process fracture, that group. Why does this occur? Well, the Superion is placed more anteriorly than the X-STOP in the spinal segment. Therefore, it's closer to the center of rotation of the spinal segment. No dislodgments or migrations were observed, and the bone contact with the device is maintained as it sits closer to the center of rotation. The device is able to resist extension and maintain the stability in this position.

The X-STOP is placed slightly posterior, as discussed, and is further from the center of rotation. This places greater risk for dislodgment and migration to occur, which can result in a loss of fixation and a loss of the extension-blocking process. And this was shown radiographically as well as by a 7.4 increase in the clinical for the spinous process fracture group for the X-STOP.

Now let's talk about the geometrical differences and the bone contact between the

Superion and the X-STOP. This, too, has a biomechanical mechanism related to the actions. The Superion has a saddle design for the spinous process. Again, it sits closer to the center of rotation. This saddle shape accommodates that specific region of the spinous process. There's less distance horizontally between the cam lobes or the wings than that of the X-STOP. So when the patient stands with axial moving, the device becomes seated between the spinous processes.

For the X-STOP, it's a cylindrical design for the spinous process. This sits further from the center of rotation than the Superion. There's greater distance between the wings of the device. So, with axial loading, upon ambulation the spinous process rests on this cylinder and it's less stable in the presence of a spinous process fracture. Therefore, it's at much increased risk to dislodgment and migration.

So, in summary, with respect to explaining the mechanism of action in the presence of a spinous process fracture, it's related to the factors shown here. Surgical technique. For the Superion, it's a minimally invasive posterior approach that allows the surrounding tissues to remain intact. By having those tissues intact, you can maintain stability across that segment.

The device design. As previously discussed, the saddle design of the Superion allows -- maintains the bone contact with the device, and the implant becomes seated between the spinous processes. Combined with the device location being closer to the center of rotation, you're at less risk than the X-STOP, for instance, of any kind of dislodgment or migration. And that was shown clinically, that there were no dislodgments or migrations.

Fracture location for the Superion is coincident with the device. Again, you still

maintained bone contact with that device and therefore maintained the ability to resist extension and maintain the stability. And the fracture behavior between the two devices differed. Again, we did not see migrations or dislodgments with the Superion, based on the biomechanical rationale presented, where the X-STOP demonstrated dislodgments and migrations radiographically and clinically.

Thank you.

MR. STIEGMAN: This is Glenn Stiegman.

I keep thinking of the questions that were asked. One was regarding tip avulsions, and these were not directly measured. They were only noted in the narrative, the surgical notes. There were only a few of those. We'd have to pull those patient IDs to run that analysis that Dr. Rao asked for. We do not have that analysis at this time.

I think this concludes all of the questions that were asked.

DR. RAO: Mr. O'Brien.

MR. O'BRIEN: I just don't know if I got the answer to the question comparing 63 to 78, in terms of the character of the fractures. There are two different fractures here that are in conjunction with the device, and one is anterior to it and one is posterior to it. And it was presented in Slide 63, that this was the majority -- the characterization of the fracture. And then the following slide, on 78, had a much different one. They did a construct of what the fractures look like. I was just trying to get a reconciliation between these two, or am I missing something?

DR. BLUMENTHAL: Scott Blumenthal.

Again, the representation in the latter slide that was created by Medical Metrics was

created from an x-ray of a different patient. No two fractures really are the same. So what was being measured is the origin of fracture was within the geometry of the implant. So that would be considered coincident, but two of them are not going to look the same. So those are two different patients.

MR. O'BRIEN: So that doesn't represent the majority?

DR. BLUMENTHAL: Well, the fracture origin was still within the geometry of the design. It just had a slightly different angulation to the fracture. I hope that answers your question.

DR. RAO: Dr. Gilbert.

DR. GILBERT: So the picture that was just up there showing the fracture in the Superion had the saddle posterior to the fracture, so that it's unlikely that that's going to provide that backstopping capability that you're asserting will occur in the midst of a fracture. So the one example you showed of a fracture at the saddle still providing that biomechanical support would not be the case in this radiograph. And so it does really raise the question of how frequent would you preserve that backstopping, the blocking of extension in the presence of a fracture.

DR. BLUMENTHAL: Scott Blumenthal again. Let me see if there is a pointer. There is a pointer.

Two ways to answer your question. This line is not the fracture; it's this line here, and we lose the fracture right as it hits the wing. So there actually could still be some contact of the saddle with the proximal spinous process because you just can't see it once it gets behind the device.

I think the other point that Lisa brought up is with the less tissue disruption implied in the technique of insertion, you're going to get some extra stability from the tissue, as well. So even in those circumstances maybe where there wasn't contact with the spinous process, the soft tissues contributed to the lack of migration, and it could still block, theoretically, once the spine is in extension.

DR. RAO: Just to follow up on that, Dr. Blumenthal. You know, the soft tissues posteriorly will not help with preservation of extension typically. The preservation of the soft tissues you're talking about, they're more useful, I think, for stability in the flexion mode. So that still doesn't -- between that answer, Dr. Gilbert's question, and Dr. Ferrara's response, I still don't have a clear understanding of what is the presumed mechanism of action of this device.

You take pains to point out that it has a different mechanism of action from the X-STOP. You're saying it's a blockage of extension as opposed to a distraction of the posterior column. But we don't get data from Dr. Ferrara's response as to how much extension is really blocked. She gave us a combined flexion-extension number without clear data on extension blockage. The amount of flexion-extension arc was decreased after insertion of Superion. So I don't have a clear understanding of what is the presumed mechanism of action of this device, if it's not to clear posterior distraction.

DR. BLUMENTHAL: The second part of your question. We kind of ran into the difficulty in working with Medical Metrics, and we asked that question, can we get the data for just extension? And there was too much inter-patient skew on the neutral position. Plus, these are pathologic spines, and preoperatively they were splinting anyway. So we

only had to go off of the data that we had, which is the total arc of range of motion.

DR. RAO: Excuse me for interrupting. But then was this a post hoc developed mechanism of action? Were you presuming that there would be distraction initially, but when you didn't have the data, you went to a secondary line of mechanism of action? How exactly did you come about this mechanism of action?

DR. BLUMENTHAL: The study wasn't designed to determine a mechanism of action. There was no definite agreed-upon mechanism of action based upon previous studies, X-STOP, for example. So the answer to your question is yes, we wanted to analyze why these patients seemed to not have their results deteriorate in the presence of a fracture. And this all, yes, post hoc analysis based upon trying to figure out why the clinical and the radiographic -- how to make them work together, so yes.

DR. RAO: Thank you for your honesty.

MR. STIEGMAN: I would also like to -- this is Glenn Stiegman -- allow Lisa Ferrara to further that conversation slightly. Because she gave our presentation, she can give the looks of mechanism of action.

DR. FERRARA: First, I wanted to address the soft tissue question that you had. In extension, the soft tissues actually do still play a role. Ligaments and the musculature in tension and compression do have a loading capacity. They are the cables and the pulleys to your spine, as you know, and that's a simplified version. But they do play a role, and when they're taut they can -- and when they're functioning and taut, they can actually absorb 10% to 15% of that load, so they can load-share with your spine. That's why if you strengthen your core muscles, for example, you can offload your spine in a degenerative situation.

Now, I understand your concern with not being able to locate the neutral region from the clinical. We did do cadaver studies -- and I know you've all read them -- where we looked at the kinematic assessment of the Superion, and what we found in these studies -- and I'm going to just briefly present the two kinematic assessments with Superion. They were with intact spinous processes, but we did have sequential compromise of ligamentous tissue, et cetera. They did both perform by decreased range of motion, which is an indicator for extension blocking.

And what we found in the biomechanical cadaveric study -- keep in mind, these are osteoligamentous spines, which would make it even more worst case because there is no soft tissue helping to load-share with the spine. We had a 40% to 50% decrease in range of motion when the cadaver spines were instrumented with the Superion, and we did a sequential transection of the posterior ligamentous tissue. Does that help address your question? We did break out extension from flexion.

DR. RAO: Thank you. That does provide more information.

DR. FERRARA: Thank you.

DR. RAO: A couple more questions. The FDA -- go ahead, Dr. Gilbert.

DR. GILBERT: Just one additional thought. This is Jeremy Gilbert.

I'm wondering, did you do any sort of biomechanical study of fracture of the spinous process in a cadaveric study? Do you have any sense of what loads are needed to induce fracture? Do you think that's something that might be worth exploring?

DR. FERRARA: Lisa Ferrara again.

No, we did not do a biomechanical study with spinous process fracture, but in all

honesty, we did -- with the transection study, we really only found a very small contribution from the supraspinous ligament when that is cut. As you know, when you're testing cadavericly, the supraspinous ligament is often compromised in flexion of an intact spine. It doesn't contribute a lot, because the device is so much stronger than the supraspinous ligament. And the interspinous ligament contributed, when intact, approximately 15%, 15% to 20% at most, but we didn't evaluate the spinous process fracture. But from an indirect assessment through the ligamentous transection study, it gives us an idea knowing that the Superion is going to be stronger than the posterior ligamentous tissue mentioned, that we were going to still be able to maintain stability and extension blocking because it would seat between the two spinous processes. Does that address --

DR. GILBERT: This is Jeremy Gilbert again.

I was mostly interested in sort of the contact mechanics problem between the spinous process and the device itself, how much contact stress is developed at the point of contact of the spinous process with the titanium surface, and could you create a stress high enough in contact there to induce fracture, and just wondering what effects there might be in terms of geometry of that contact, the moment arm or moments developed that might induce the fracture of the bone, not failure of the implant itself.

DR. FERRARA: Well, I guess if we looked at it when we discuss in the presence of a spinous process fracture, just the natural fiddling that occurs with that segment, you still have -- because the fracture is coincident with the device, you still have an intact piece of bone that is seated within the saddle region. With the settling that would occur with ambulation, the axial load, for instance, you're basically going to have more of the spinous

process seated in the saddle. What happens at that point is you've got greater load-sharing within the device. So you've got the saddle and the two cam lobes, and you're going to have less stress transferred because more of the load is being shared with that saddle. Even with the small amount of settling that would occur from ambulation, for instance, you'll have less stress transfer in the cam lobes and less stress transfer to the surrounding spinous process.

DR. RAO: Dr. Lyman.

DR. LYMAN: Yes, just a couple points of clarification. One, thank you for your finding that *Spine* (2006) article with the MCID and the U.S. population, but what I was actually asking is if you had calculated it internal to your own study. Those are patients maybe with the same underlying disease state, but they're still not the patients that ended up in this study, as I understand. And so whether or not you have calculated MCID internally, which is typically how those are done.

MR. STIEGMAN: Glenn Stiegman.

We did not calculate that.

DR. LYMAN: Okay, thank you. And the second point that I wanted to make was when I asked about PROMs proximal to the fracture, time of fracture. I appreciate you showing that graphic where you show it over time, but that still doesn't break out for the specific fracture the next PROM that they filled out, and that's what I was interested in, is whether or not that's where -- if the differences exist there. My suspicion is that it's not, but you didn't quite answer the question that I asked before.

MR. STIEGMAN: Yes, I think the only time points we have are those obviously

collected in the study. So, if a fracture happened in between that time point, the next time the patient comes in, if they were to come because of pain, then that would be noted as an adverse event.

DR. LYMAN: Okay, I see. Thank you.

DR. RAO: Thank you, Dr. Lyman. Thank you.

There are a couple of questions that the FDA kind of punted to you somewhat conveniently for them.

(Laughter.)

DR. RAO: So I'm going to ask you to kind of clarify and give the Panel some better understanding of these issues. One of the questions was Tables 9 and 10 in their submission to us that we received before the meeting. There's the incidence of the leg pain quoted in Table 9. It has about 20% in the Superion group. But in Table 10, that talks about leg pain specifically related to the device; it was just one patient. So the question is how did you ascertain that this one patient had leg pain related to the device, and the remainder of that 20%, their leg pain was not related to the device?

MR. STIEGMAN: This is Glenn Stiegman.

The difference in numbers was responded to by the FDA and that one is all adverse events and one is device-related adverse events. As far as that one being related to leg pain, that's the job of the CEC to properly adjudicate all of the events in that fashion.

DR. RAO: Would you repeat that again?

MR. STIEGMAN: The job of the CEC, the clinical events committee that looks at all possible and device-related and procedure-related adverse events, adjudicated all adverse

events, and that's how they believe it was properly denoted.

DR. RAO: But I think the Panel needs some clarification as to why your CEC felt that that one patient was related to the device and the remainder were not related to the device.

MR. STIEGMAN: I'm going to ask Dr. Geisler to come up.

DR. RAO: Thank you.

DR. GEISLER: In detail, I cannot remember all of them right here, but what we can do is pull that chart out, re-review it, and respond to you in writing shortly.

DR. RAO: Thank you.

Dr. Trier.

DR. TRIER: Just a quick question. This is Dr. Trier.

Dr. Geisler, there were probably some parameters that were used as a decision-making factor to determine whether it was device related or not. Are you able to share what those parameters would be? Like what would you look for in a patient chart?

DR. GEISLER: Well, there would have had to be something in that chart that made us think that it was more directly related. We also get our cues from the investigator, as to what the investigator's opinion was, but the three of us would then readjudicate it to try and add uniformity. But in a specific example, I'm sure I can come up with something, but I'll have to look at our actual notes and the charts from that in order to do that. It's a good question, and we'll just have to pull the charts and get back to you.

DR. RAO: Thank you, Dr. Geisler.

I'd just like to follow up with Dr. Melkerson. Dr. Melkerson, would it be acceptable

to have that information provided to the Panel in writing at a subsequent date, if we are still expected to respond to the questions that the FDA has and provide some kind of voting process before we have that information?

MR. MELKERSON: Unfortunately we have to go with what is already contained in the PMA to date. So, if that information isn't available or clear, it's based on what information you have to date. We can ask for that subsequently, in light of what your recommendation would be, but that may be something that we would have to follow up after the Panel.

DR. RAO: Thank you, Dr. Melkerson.

MR. STIEGMAN: Can I provide one point of clarification?

DR. RAO: Please.

MR. STIEGMAN: This is Glenn Stiegman.

The CEC was given a lot of information, the patients' VAS scores, leg pain, back pain, ODI, ZCQ. So they had a more complete picture of the adverse events and could adjudicate it appropriately based on what they saw. So, if the VAS leg pain score had declined significantly, they could adjudicate that pain event as being leg related.

DR. RAO: Thank you. Another follow-up question on a theme that Dr. Yang raised, which is the revision procedures that were carried out because of spinous process fractures. To this point we've generally felt that the spinous process fractures may be clinically benign. But if we have four patients who required revision surgery "because of the spinous process fracture," that raises some level of concern. So could you please explain to the Panel why these four patients needed revision surgery because of the fracture and the remaining 27 patients or the other tip fractures did not need revision surgery?

DR. BLUMENTHAL: Scott Blumenthal.

You know, as you can imagine, it's difficult in a patient with acute or early postoperative back pain to know whether for sure or for certain whether the spinous process fracture is indeed the cause. But if there is a fracture there and they have back pain and you feel that there's something you need to intervene, that's probably the low-hanging fruit to say, okay, that's what's causing it. It may or may not.

I think the obvious reason why the other ones weren't revised is that they didn't have symptoms that the treating doctor felt were appropriate or ascertainable or pertainable, I mean, to the fracture itself. I don't know that we can get the exact information because back pain is a pretty nonspecific complaint, so it's left up to the judgment of the treating surgeon as to whether or not it needs to be revised and whether or not he or she is going to attribute it to the fracture or just it could be some other pain generated.

DR. RAO: Thank you.

Dr. Alander.

DR. ALANDER: On page 36 you report a dural tear. I'm just wondering if that had anything to do with this leg pain.

MR. STIEGMAN: Glenn Stiegman.

It could. I'd have to look at the whole big picture of that patient. That very well could be the cause.

DR. RAO: Mr. O'Brien.

MR. O'BRIEN: Joe O'Brien.

I just had a question. From 24 to 36 months, we had a 30% increase in reoperations and representing about 7% of the population at that time, was considered success at that time. I don't know if there's any data. Were any of those related to fractures? Or were they fracture patients, patients with fractures?

MR. STIEGMAN: It is unclear. I can find out, of those that were reoperated between that time point, if they are fracture patients or not. There were no new fractures in that time period.

MR. O'BRIEN: But you don't know whether or not they were -- I'm interested in are they fracture patients.

MR. STIEGMAN: Right. Keeping in mind that those patients that were not healed, had the fracture not healed at 24 months, were already considered failures.

DR. RAO: Dr. Graf.

DR. GRAF: One comment/question. In considering your surgical approach of splitting through the interspinous ligament, are we in fact transecting that ligament in some respects, dilating the sub and inserting a large device? Operating on patients on a weekly basis and doing this, I find it difficult to imagine that I can split through the interspinous ligament and insert this device without somehow compromising it.

DR. NUNLEY: Pierce Nunley.

Dr. Graf, I think your question and observation is a valid one. Certainly it's complex and it's a wide ligament, and it's also variable in patients. But definitely being in surgery and feeling after pulling the cannula out, there's still an intact ligament there. I'm sure fibers of that have been compromised, but it's not like when you go into an extension

fracture environment and you see a hole there. I mean there's still an intact ligament to your finger. And some sites chose to put a suture and some didn't. I was one that didn't because I felt that there was a strong enough ligament therein lying with those fibers.

DR. RAO: Just some more clarification. If L5-S1 was not included in the study population, does it reach the threshold of being included as an exclusion criteria for this device?

DR. BLUMENTHAL: Scott Blumenthal.

Yes.

DR. RAO: So you will change the exclusion criteria to list that, because it's currently not listed as an exclusion criteria.

DR. BLUMENTHAL: If I remember correctly, the inclusion criteria is to be used from L1 to L5.

DR. RAO: Correct, but it's not --

DR. BLUMENTHAL: So I guess the implication is L5-S1 would be excluded, but yeah, that could be labeled in.

DR. RAO: Because it's not entirely spelled out or clear. If someone is just looking at lumbar spine, they may miss that.

DR. BLUMENTHAL: Yes.

DR. RAO: Dr. Gilbert.

DR. GILBERT: I'm thinking back on a comment, I forget who made it -- perhaps it was one of the public speakers -- about the difference in a surgeon who's part of the center study and a surgeon who is just a regular surgeon using this device, and I'm wondering if

your post-approval study plan intends to bring in a wider range of surgeons to assess that variability.

MR. STIEGMAN: This is Glenn Stiegman.

Yes, I think that's an ideal scenario for an actual conditions of use study, is to make sure it performs as well as we think it can. The risk mitigation factors are taken into account in a broad area of different types of surgeons.

DR. RAO: Thank you very much, all. I think -- Dr. Golish.

DR. GOLISH: The question is for Dr. Nunley, and I'll admit, it's sort of a big picture clinical question. So, if you feel it's sort of outside of your purview as a consultant, I'd respect that.

DR. RAO: It's part of that same sticky wicket.

DR. GOLISH: Yeah.

(Laughter.)

DR. GOLISH: So, in your current busy clinical practice of the patients that you have with moderate stenosis who sort of fit the inclusion/exclusion criteria of this trial, how many of them are getting microsurgery in your hands, and how many of them are getting an interspinous process device? Not a trial device, a commercial device, X-STOP being the only one available. That was the first question.

But then the follow-on really is that, even though this is a non-inferiority trial, it doesn't preclude the possibility of some advantages. The second question is what are the advantages you'd be seeking to make such a device more compelling to get your patient a good result and spare you an hour of microsurgery in the process?

DR. NUNLEY: That's a very good question, and I would first state that in my practice and the patients that come in with moderate stenosis, one of the comments made by the public was speaking to the fact that X-STOP seems to not have a great deal of favor, and there are many reasons for that. And I can tell you, one of the reasons in our marketplace is the hospitals and the reimbursement and the negative push for that. So I will say that we have -- my hospital wouldn't pay for the X-STOP, so it wasn't available. So I do still use X-STOP. Now it's available and I use it once or twice a month, but the majority of patients still get a microscopic lumbar decompression.

I think there's a difference, too, and part of it is, is that once you see what else is out there, I think there's a difference between the X-STOP procedure and Superion, and Superion is less invasive. Quite frankly, assuming it gets approved, I see in my practice that I will be using it more frequently as an interspinous process device and my ratio of using an interspinous process device to microsurgery will go up. Did that answer your question?

DR. GOLISH: Thank you.

DR. RAO: Dr. Carrino.

DR. CARRINO: My question is do you think it matters if the spinous process fracture is anterior or posterior to the lobes, either biomechanically, symptomatically, or having to do a revision?

DR. BLUMENTHAL: This is Scott Blumenthal.

I can answer it clinically. No, I don't think it makes a difference.

DR. RAO: Anyone else with a question for the FDA or for the Sponsor?

(No response.)

DR. RAO: Very good.

I think we'll keep working right now, we'll keep going ahead. We're going to go ahead with the FDA non-voting questions at this point. Panel members, copies of the questions are in your folders. After the FDA states each question, we will go around the table and ask all Panel members for their response to this FDA non-voting question. I will change the order around so not everyone feels like they're being penalized with the first answer. But at this time, I would ask that each Panel member identify himself or herself each time he or she speaks to facilitate transcription.

Dr. Wyatt, could you please show us the first question at this time?

DR. WYATT: Okay, they should be up.

Two radiographic success elements were included in the "absence of major implant or procedure related complications" subcomponent of the primary composite endpoint defined in the IDE protocol. Both the Superion and X-STOP cohorts had similar results at 24 months for this subcomponent (i.e., 88.9% and 86.1%, respectively); in other words, 11.1% of Superion subjects and 13.9% of X-STOP subjects experienced a major implant or procedure related complication. However, the majority of failures in the Superion cohort were due to spinous process fractures (n=31 at any time point), while the failures in the X-STOP cohort were primarily due to migrations (n=16) and dislodgements (n=20). Spinous process fractures (n=17 at any time) also occurred in the X-STOP group. Please discuss the potential clinical impact of the different types of radiographic failure modes (i.e., spinous process fracture, migration, dislodgement), as well as the appropriateness of comparing them in determining radiographic success, and consequently, overall success.

DR. RAO: So let's start with Dr. Trier, on your side. Dr. Trier, do you have any thoughts on the potential clinical impact of these different types of radiographic failures, as well as the appropriateness of comparing them in determining radiographic success?

DR. TRIER: With regards to comparing them for radiographic success, I guess I would defer to whether or not there is a clinical impact. We see many things on radiographs that may not have an impact on how well a device may or may not do clinically. And so from my standpoint, it seems to me that things such as dislodgment and migration would have a more serious clinical impact than a spinous process fracture.

DR. RAO: We'll go to Mr. O'Brien.

MR. O'BRIEN: Joe O'Brien.

Well, certainly I'm not a clinician, so it's difficult for me to discuss that aspect of it. I do worry, though, again looking at where the location of these are relative to the device. The population that we deal with in the adult population with degenerative conditions is continual physiological changes with flexion that's going to take place, and as I see these, you know, despite what I hear in the biomechanics, I quite honestly think that this is a patient that's going to be back 10 years from now and needing procedure. It's not a matter of if, it's a matter of when, and I'm not quite sure if that's what the intent of this device is, to be a bridging mechanism, or if it's intended to be a long-term one-time device.

DR. RAO: Thank you, Mr. O'Brien.

Dr. Yang.

DR. YANG: Lynda Yang.

So the question that I see here is a question of potential clinical impact of the

different types of radiographic failure modes. So, frankly, in my own practice, the clinical impact of a spinous process fracture is minimal to none. Again, you know, if -- the migration and dislodgement, that's a different issue because if you're relying on the migration and dislodgement to create that extension or prohibit extension, then it may be more significant. So, frankly, if the direct question is, is spinous process fracture on a radiograph, especially an x-ray, which we all know depends on the mineralization, et cetera, et cetera, going to have a clinical impact, I would have to say very little, if any.

DR. RAO: Dr. Lyman.

DR. LYMAN: I actually have nothing to add. I think I would echo what Dr. Yang said, that it seems to me -- and I'm an epidemiologist, not a clinician -- that the device moving away from where it's supposed to be is more concerning than an asymptomatic spinous process fracture.

DR. RAO: Thank you.

Dr. Graf.

DR. GRAF: In taking Dr. Yang's point, that spinous process fracture in and of itself in our clinical practice, outside of this device and this mechanism, I completely agree. What I can't wrap my mind around is that this product and any interspinous device product relies upon the distraction in order to have the result of indirect spinal decompression, which if there's a spinal fracture and -- there's a spinous process fracture, rather, and there's a shifting of that, I can't fathom how that does not impact the clinical result.

DR. RAO: Dr. Carrino.

DR. CARRINO: I think there's a categorical difference in the different types of

radiographic failure modes, so if a device is migrated, it could still be functional if the migration is minimal. If it's dislodged and presumably it's nonfunctional because it's not in the appropriate position that the operator intended and then a spinous process fracture, I think, may or may not have an implication. But depending on whether it's anterior or posterior to the lobes, because if the device is still distracting the spinous processes but the spinous process fracture is posterior, it could still be providing its function, whereas I think if it's anterior, it's not.

DR. RAO: Thank you, Dr. Carrino.

Dr. Alander.

DR. ALANDER: I think migration and dislodgement are the two concerns I would have over spinous process fracture. And I think spinous process fracture would really depend on whether or not they're having clinical symptoms. They may, in fact, collapse down; they're going to have clinical symptoms. If they don't collapse --

DR. RAO: Thank you, Dr. Alander.

Dr. Haines.

DR. HAINES: Yeah, Steve Haines.

It certainly complicates the situation. This is a somewhat unexpected result. It's natural to say that dislodgement and so on obviously should make the device ineffective at that point. But the spinous process fractures, most of which were either with the device or in front of it, certainly call into question our understanding of the mechanism of action of the device. And it may well be that the duration of follow-up is simply not long enough to see what the impact of those changes are, so it makes it a little more difficult to understand

the device, its effectiveness, and so on. It would be really ironic if, in the end, the clinical benefit turns out to be relatively small and we've converted a clinical nonentity, spinous process fracture, from a nonentity to something that we have to worry about.

DR. RAO: Thank you, Dr. Haines.

Dr. Golish.

DR. GOLISH: I don't know what batting cleanup in cricket is called, but I guess that's what I get to do. Yeah, I certainly agree that the Sponsor presented information that the clinical sequelae of their fractures seem to be relatively benign or at least not pernicious. I certainly agree that migration is a worse problem. That said, even in the patients who have a fracture that were counted as failures, the continuing mystery about what can the mechanism of action be in that patient is a little bit hard to reconcile. I think that it stands to reason that the fracture was created by loading those elements with the device, and it's harder to understand how the device will continue to provide all the distraction that it might in the presence of that. And I think that's further compounded by the scrutiny that the concept of posterior distraction alone continues to be under as a clinical concept as time has gone on.

DR. RAO: Thank you, Dr. Golish.

Dr. Gilbert.

DR. GILBERT: So there are the unknown unknowns, right, and I suppose here that the biggest sort of question mark I have is that the spinous process fractures were, I think, not really anticipated. It doesn't seem to me to have been anticipated. And so, therefore, the consequences of those fractures have not also been fully anticipated. And as I think

some of my colleagues here have alluded to, there may be consequences to those fractures that we haven't thought of because we haven't seen an example of it. Could the device migrate as a result of a displaced fracture of the spinous process? Could that migration, then, present a potential impact on a nerve root or some other structure adjacent to it?

And so those are unknowns that I think are raised; questions are raised about them because of this fracture mode showing up. And so I think also it behooves the company to try to understand the source of that fracture and perhaps look at ways to mitigate it in the design or the materials or the mechanism of deployment or some other element.

DR. RAO: Thank you, Dr. Gilbert.

Mr. Melkerson, with regard to Question 1, the Panel generally believes that spinous process fractures may have limited clinical consequences from the fracture itself in many situations. However, the fracture may be an indication of increased loading in the posterior elements and may suggest that the distraction that was originally gained by insertion of the device is lost. That loss of distraction may result in subsequent clinical effects that are not entirely clear at this time. There is question as to whether the device will be effective long-term or whether it will act as a temporary bridging device. The Panel also believes that migration and dislodgement of the device would generally be a more serious consequence or of more significant consequence than spinous process fracture.

Mr. Melkerson, is that adequate?

MR. MELKERSON: Yes, it is. Thank you for your input.

DR. RAO: Let's go to Question 2.

DR. WYATT: During the course of the clinical study, the patient incidence of spinous

process fractures observed in the Superion and X-STOP cohorts were 16.3% and 8.5%, respectively. At 24 months, 32.3% of the Superion fractures and 41.2% of the X-STOP fractures exhibited signs of healing as described by the sponsor. In addition, the sponsor provided an analysis of ZCQ, ODI, VAS Leg and Back scores to support their conclusion that most of the spinous process fractures in both groups were asymptomatic.

a) Please discuss the clinical significance of the observed spinous process fractures, particularly given that interspinous process devices rely upon intact spinous processes to exert their treatment effect.

b) Please also discuss the analysis presented to assess the correlation between spinous process fractures and effectiveness (i.e., ZCQ, ODI, VAS Leg and Back) outcomes at 24 months with particular focus on whether the analysis is adequate to determine the clinical significance of the observed spinous process fractures.

DR. RAO: Thank you, Dr. Wyatt.

Let's switch the order here a little bit. Dr. Carrino, if you could respond to the FDA's question (a) and (b) separately, please?

DR. CARRINO: I'll try. So I think the way I understand (a) is that "discuss the clinical significance of the observed spinous process fractures," and the way I would frame it, and frame it for the first question, is that in the clinical context of somebody coming in with symptomatology or pain, you then look at imaging to see if you can get any insight as to why they're having persistent symptoms or pain. And so then, in that context, if somebody's coming back with -- doesn't have the treatment effect or has worsening symptoms or different pain, then I think those fractures could be significant.

And then (b), I would defer the analysis part to people who understand the methodology better.

DR. RAO: Thank you, Dr. Carrino.

Dr. Alander.

DR. ALANDER: So I think that the clinical significance really rests on where the person will be at, at a certain point in time, postoperatively. Along the same line of analysis, if somebody comes in early postop, there's expected back pain from the surgery; I wouldn't really explore that. But at 6 weeks, when they should be declining, if they have continued problems, then I would look for spinous process fracture and then follow that up.

DR. RAO: Thank you. And for part (b), do you have any additional thoughts?

DR. ALANDER: I'd have to defer again.

DR. RAO: Dr. Haines.

DR. HAINES: Steve Haines.

I think we've discussed (a) pretty thoroughly in answer to the first question actually. Anytime you do an analysis on what is essentially an unexpected result, you have the problem that you couldn't plan it in advance, so I think that's a problem. And, again, I think that the duration of follow-up for this particular problem is probably not long enough to know the ultimate implications.

DR. RAO: Thank you, Dr. Haines.

Dr. Golish.

DR. GOLISH: I agree this encapsulates on what we've already discussed. But, briefly, the clinical significance, I think, remains to be seen because the mechanism of action

ostensibly depends upon distraction loading, which must be compromised to some degree in the fracture.

With respect to (b), I think the Sponsor has shown data that demonstrate that in their trial the clinical sequelae are not very well correlated with the fracture itself, and they were counted as failures, so I think they've done what they can be expected to do with respect to (b), but I think significant questions still remain with respect to (a) in the clinical future. And unlike the coflex device, for example, which maintains significant interference and loading on the lamina, you know, the absence of an intact spinous process fracture continues to raise the question of mechanism of action, which was raised a number of times.

DR. RAO: Thank you, Dr. Golish.

Dr. Gilbert.

DR. GILBERT: I only have one small thought to add to this. In the part (b), the majority of the fractures showed up between surgery and 6 weeks, and really you can read that as between surgery and Day 2 or Day 3 because you haven't taken an x-ray at Day 2 or Day 3, so you don't know did those fractures occur the first time they stood up or the first time they stepped off a curb or whatever happened; it was only after 6 weeks. And so I think that that intervening period from 0 to 6 weeks and how the fractures developed should be investigated.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Graf.

DR. GRAF: Again, I reiterate. I believe that we covered most of this in the answer to

answer number 1 as well. As far as the clinical significance, as has been stated, I think that that will pan out over time with longer-term studies, and if this is truly a bridging device or not, I don't believe we can determine that right now.

DR. RAO: Thank you, Dr. Graf.

Dr. Lyman.

DR. LYMAN: I have nothing to add for Question 2a.

For (b), I spend most of my time thinking about patient-reported outcomes, and I'm not at all convinced by the analysis that's been presented today both because it's underpowered and because of the way that it was presented, whether or not a difference actually exists. Based on the comments from my clinical colleagues, it seems like maybe it doesn't matter, at least if you don't have a device implanted; these fractures are clinically insignificant. But in the presence of a device, I'm still not convinced this is the appropriate way of measuring whether or not there is an effect on the effectiveness for the patients. I'm also just not sure that these instruments are sensitive enough to pick up differences that might exist if differences do exist.

DR. RAO: You mentioned two factors. One was underpowered. What was the other factor?

DR. LYMAN: Just the sensitivity of these instruments to actually --

DR. RAO: Okay.

DR. LYMAN: -- pick up differences in effectiveness in this context.

DR. RAO: Do you have any suggestions as to any other instruments that should be used or should use patient-reported outcomes?

DR. LYMAN: I mean, PROMIS is showing promise.

DR. RAO: Okay.

DR. LYMAN: You know, they've already done the study.

DR. RAO: Thank you.

DR. LYMAN: Sorry, one more comment.

DR. RAO: Sure.

DR. LYMAN: It's possible that individual questions within the instruments could be more sensitive rather than the overall scores, the summary scores.

DR. RAO: Thank you, Dr. Lyman.

Dr. Yang.

DR. YANG: So, with regard to (a), the second part that says given that interspinous processes may rely upon the intact spinous processes to exert the treatment effect, I think that statement is probably a little bit hazy, like there is no -- nothing that tells me that's the mechanism. So we've already talked about, you know, the lack of clinical significance from my standpoint, at least, for part 1, so -- as far as part (b) goes, I'm just glad Dr. Lyman spoke before I did. From what I gather, I don't think there's enough information to attribute either positive or negative clinical outcome because of a spinous process fracture.

DR. RAO: Mr. O'Brien.

MR. O'BRIEN: Joe O'Brien.

Just reiterate what I said in the first question regarding (a), except I would add when, you know, as I have to, when I'm talking with patients, I look a little bit different in the introduction that is here in the sense that I don't see 32% healed; I see 68% didn't heal,

because the patients, when they are referring to us and they're in pain, it's the ones that didn't heal. So I see 68% didn't heal. So, therefore, I look at that, that that still sort of supports my concern that I expressed in the first question about what's going to happen to this patient in the clinical significance of those fractures relative to the device. I understand fractures by themselves aren't, but relative to the device, I still have concerns with that.

Regarding (b), again, I'm not an expert on -- I know these are validated patient outcome instruments, and I respect that, except I would say that with 10,000 patients, no one has ever known what their ZCQ scores are or what the ODIs are or et cetera. I know it's just relative to their pain, their quality of life, mental health, and other things that really weren't discussed as part of this even though they're low, et cetera. So these are the things that I would deal with, so I'd still have concern about them, so -- I'm not quite sure. We have never found, as a subjective issue, that these instruments have been really good in terms of -- you know, some will fill them out, and then the next minute, when they're in talking to someone else, it's a totally different answer.

DR. RAO: Thank you, Mr. O'Brien.

Dr. Trier.

DR. TRIER: Yes, this is Dr. Trier.

And I really don't have anything to add to letter (a), to the question letter (a), but with regards to letter (b) having to do with the scoring, using the standardized assessment tools that are there, you know, one of the things that is of benefit using those tools in a clinical study of this type is the fact that you can compare across devices. You know, when we use standardized instruments like that, that have been validated, it does make a

difference. You can use things that, you know, may be a single question off of a questionnaire or whatever, but if you went to look at the composite and how this device compares to another device like the X-STOP, you really are forced into using these types of evaluation tools.

So, with regards to question (b), I believe that the data that's presented and the analysis that is presented using these assessment tools does, in fact, demonstrate that it's an adequate analysis to be able to show that this device is, in fact, non-inferior to the other devices regardless of whether or not there are spinous process fractures.

DR. RAO: Thank you, Dr. Trier.

Should we respond to these two first before we change the slide?

DR. WYATT: We can.

DR. RAO: Thank you.

Mr. Melkerson, with regards to Questions 2(a) and (b), with regards to Question 2a as to the clinical significance of the observed spinous process fractures, the Panel generally feels that the spinous process fractures themselves may not be a huge clinically significant issue. However, the long-term consequences of the spinous process fractures that are created by the device and any potential loss of efficacy of their presumed mechanism of action is unclear at this time.

With regards to question (b), which deals with whether the analysis was adequate to determine the clinical significance, the Panel generally feels that while the instruments used may be helpful in comparing the results of this study with previously carried out studies, the instruments may not lack the sensitivity and may not be patient focused enough, patient

reported enough to provide adequate information as to whether the spinous process fractures have a clinical effect on the patient in the short or long term.

Mr. Melkerson, is this adequate for parts 2(a) and (b)?

MR. MELKERSON: Yes, thank you.

DR. RAO: Dr. Wyatt.

DR. WYATT: So this is a continuation of Question No. 2.

The diagnosis of spinous process fractures in this clinical trial were made by plain radiographs, and when comparing the treatment groups, there was a disproportionate discrepancy between the investigators and core lab in identifying the number of spinous process fractures. Recent literature suggests that spinous process fractures related to interspinous process devices are under-recognized, and recommends the use of CT scans for a more accurate diagnosis. Please discuss the utility of CT as compared to plain radiographs in the diagnosis and classification of spinous process fractures after treatment with an interspinous process device, as well as in the assessment of bony healing of fractures that are identified. In addition, please discuss the most appropriate time point for conducting these imaging studies.

DR. RAO: Thank you, Dr. Wyatt.

I did give him enough warning ahead of time, but I'll start with Dr. Graf.

DR. GRAF: So, to answer the question, if we're to use CT scans, this would of course be much more sensitive in detecting these fractures. And I think that looking at the numbers in the study, likely some of the fractures that were detected weeks out, that will likely shift to closer intraop, because personally, they're likely involved with operative

technique and operative placement and initial loading of that spinous process. In my mind, as I mentioned earlier, CT scans at regular intervals on patients, though, would pose or bring forward the issue of radiation of these patients who are undergoing these studies, so I think that that has to be considered. In my opinion, overall, the clinical outcome would be more important than a radiographic diagnosis of a fracture via CT.

DR. RAO: I'd just like to clarify, Dr. Graf. When you used the word "radiographic," you're specifically referring just to the CT scan and not all x-rays or other modalities?

DR. GRAF: Correct.

DR. RAO: Thank you.

Dr. Gilbert. Dr. Lyman, I'm sorry.

DR. LYMAN: You switched it up on me. So I actually would like to hear Dr. Carrino's opinions about this as far as the imaging goes, but from what was presented earlier, it does seem like if you have multiple x-rays during the assessment, that's how the core lab was able to identify these fractures more frequently than the investigators. And I'm wondering if that would be sufficient relative to CT in this context for research, especially given that these fractures, at least from what I understand, are of questionable clinical relevance.

DR. RAO: Thank you, Dr. Lyman.

Dr. Yang.

DR. YANG: I don't have much to add to what Dr. Graf and what Dr. Lyman said. Yes, you can detect these better on CT, but to what end? And exposing all these patients to that kind of radiation probably isn't indicated unless you're going to be able to set up an association or causation between a spinous process fracture or failure. So frankly -- and

then there's a second part. I don't know if you wanted that or not: time point. I agree with Dr. Graf and Dr. Gilbert. You know, most of these are right at the front end. So either, you know, the day after like we often do for our fusions or -- you know, the first time they stand up or whatnot, first time they put axial load on it, it probably is a very reasonable way to go.

DR. RAO: Thank you, Dr. Yang.

Mr. O'Brien.

MR. O'BRIEN: Joe O'Brien.

It seems to me that the question at hand is what happens to the fractures that we see and identify, which seemingly quite well with the x-ray, in terms of the efficacy of the device and more importantly the risk-benefit of the device. And at this point in time, it does not seem to be appropriate to add more risk to the patient by doing a CT scan just to find more questionable fractures as to whether or not there's a clinical significance, so I don't see that as being the priority at the moment.

DR. RAO: Thank you, Mr. O'Brien.

Dr. Trier.

DR. TRIER: Yes, Dr. Trier.

I have nothing to add. I'm in agreement with all of the previous speakers.

DR. RAO: Thank you, Dr. Trier.

Dr. Gilbert.

DR. GILBERT: I'll second that motion. I have nothing more to add other than the earlier time point assessment.

DR. RAO: Dr. Golish.

DR. GOLISH: I think that in a postmarket surveillance study, it's an unreasonable risk to a large cohort of patients to require or imply that CT scans are essential. In a pivotal study and the follow-up from a pivotal study, I think the additional sensitivity is helpful especially with respect to this question of healing of an interspinous process fracture, especially in the context of stress shielding associated with an implant, I think will be hard to determine otherwise.

DR. RAO: Dr. Haines.

DR. HAINES: Steve Haines.

With respect to conventional CT and lumbar spine, I would agree with everybody. However, if it's possible, and I think it is, to come up with a much more focused CT that reduces the radiation down to levels consistent with normal practice, I think we need to ask the question whether the fracture issue might even be bigger than is disclosed by the conventional radiographs. So a targeted reduced radiation form of imaging, if it's possible, might be a very wise thing to do.

DR. RAO: Thank you, Dr. Haines.

Dr. Alander.

DR. ALANDER: Dr. Alander.

I would not recommend CT scan on a routine basis. I do take your point, Dr. Haines. I think if a patient is clinically symptomatic and you're trying to get the basis of it, I think a limited CT scan may be of use in a future study.

DR. RAO: Thank you, Dr. Alander.

And now we get to the radiologist, Dr. Carrino.

(Laughter.)

DR. CARRINO: Thanks.

So I think it brings up a number of interesting imaging issues and questions, so with regards to this rather complex question, the discrepancy between the investigators and the core lab, I think, could be related to observer performance; so observers who are trained to look for these things and scrutinize them would have a better detection rate, i.e., the value of radiologists, I presume, looking at the radiographs. In terms of the recent literature, so those -- there are two articles I found in the literature related to the detection of these interspinous process fractures in the setting of interspinous process devices, both of which were related to the X-STOP device, and the images they showed in the literature, I would say that radiographic quality was relatively poor, so radiography is harder to quality control, let's say, than CT scan. So having adequate radiography quality, I think, would enhance the detection of these fractures.

There is no -- the American College of Radiology has accreditation guidelines for a number of modalities, but there are none for radiography. And as you might imagine, if -- radiography used in the community or other practice settings may not have the same quality control as if you specify a high-quality radiograph. The other observation from those studies is that in the X-STOP device, the profile, the lateral side profile, is a little bit larger, so it could -- it's more likely to obscure a fracture line than we have with this Superion device. So I think you're more likely to see a fracture on radiography with the Superion device because of the smaller size of the lobes vis-à-vis the X-STOP device. And, also, the fractures tended to be displaced by about 2 mm, so that will improve the

detection rates. With regards to --

DR. RAO: Sorry. Could you just expand on that a little bit?

DR. CARRINO: Sure.

DR. RAO: So x-ray would improve the detection rates because of the bigger lobes or CT would?

DR. CARRINO: No, sorry. To clarify, the -- CT would be more likely to detect the fractures in the X-STOP group because they have bigger lobes.

DR. RAO: Oh, okay.

DR. CARRINO: I think the issue around CT -- so CT would be a more sensitive way to pick up these fractures. When is it exactly warranted? I think, in my opinion, if there were new symptoms that would warrant a clinical evaluation at that level, you could do a CT scan at that level to minimize the radiation exposure. Unfortunately, to do a CT to get a good evaluation, we do have to increase the dose, but it could be limited to the levels of interest. So I don't think it's necessary as a screening modality, but to investigate somebody with symptoms, I would like to dispel a little bit about the radiation issues that people are concerned about radiation, particularly with regards to carcinogenesis; it's probably a bit overstated for this age group, so that's not really a concern in my mind.

DR. RAO: Just to pin you down a little bit, Dr. Carrino --

DR. CARRINO: Sure.

DR. RAO: -- since you are the radiologist for us here, would you go back to your basic science days and tell us what is the radiation exposure for maybe a limited CT scan through the area versus maybe an A/P flexion-extension radiograph of the lumbar spine?

DR. CARRINO: Okay.

DR. RAO: Approximately is fine. Approximately.

DR. CARRINO: I do have some information on that.

DR. RAO: Or three views of the lumbar spine: A/P, lateral, and a cone-down or something like that.

DR. CARRINO: So, for an average CT scan, we're talking about what's listed as 10 mSv.

DR. RAO: And is that for a full CT of the lumbar or a more limited -- is it possible to reduce that with a more limited CT scan?

DR. CARRINO: It's probably possible to reduce it; this is the "average" CT scan. So CT has more radiation, and the area that we're looking at is closer to some critical organs, potentially like near the gonads. So it's about 10 mSv to 1 mSv. So there is an order of magnitude difference.

DR. RAO: So 1 is for the x-rays?

DR. CARRINO: One is for the radiography part, yeah.

DR. RAO: Three x-rays or -- okay.

DR. CARRINO: Or about -- yeah, probably about two views.

DR. RAO: Dr. Graf has some data on that, so I'll just let him read it out.

DR. GRAF: I just looked it up on the FDA website. Although it doesn't -- you know, we're talking about an image sequence that's really honed down to one or two levels, a CT scan of the head versus CT scan of the abdomen versus a chest x-ray or a lumbar spine x-ray. Lumbar spine x-ray was 75 mSv versus CT scan of the abdomen was 400, versus CT

scan of the head, about 100.

DR. CARRINO: So those comparisons are different areas, different organs that have different considerations. Your head has a skull, which is relatively radio resistant, so I would certainly state that the CT scan is higher, CT scan of the lumbar spine is a much higher dose than radiography. But if there is a symptomatic reason for investigating that level, I feel that the risk-benefit ratio is such that you would want to do that. I think this question gets toward, are we going to use CT as a more sensitive way to detect these fractures for the simple rate of detecting them for research purposes and for potentially downstream relevance? And I think the consensus is that we would use high-quality radiography and then limit CT usage.

DR. RAO: Thank you very much, Dr. Carrino.

Mr. Melkerson, with regards to Question 2c, the Panel generally believes that in the vast majority of patients, the concerns that may exist with radiation exposure should preclude the use of CT scans in a routine fashion for the diagnosis and classification or treatment effects for spinous process fractures. However, there may be a limited subset either based on pattern of fracture or clinical symptomatology, yet to be determined, where the use of a more limited CT scan may provide us more information on how these devices work and how we may anticipate that they will continue to work and how the functioning of the device changes as a result of the fracture.

Mr. Melkerson, is this adequate?

MR. MELKERSON: Let me ask a couple of clarifying questions.

DR. RAO: Please.

MR. MELKERSON: I heard, in terms of symptomatic, and to me, that sounds like a viable option. But what if you have already, by the standard radiographic methods, detected a fracture? In a -- and I'll say post-approval study-type mode, in terms of a study design, would it be appropriate to investigate those that were detected with a fracture, doing a CT of those? In other words, only screen if you've already detected a fracture.

DR. RAO: Yeah. So instead of saying symptoms or some other undefined micro-group, just say if someone has a fracture on the x-ray, we should go ahead and get a CT scan of this fracture?

MR. MELKERSON: That's what I'm asking, yes.

DR. RAO: I have my thoughts, but I'm going to just quickly go around the table so I don't just give you my thoughts. And just give me, in two or three words, if anyone has any thoughts -- I won't ask everyone. But if anyone has thoughts on this, please raise their hand and -- Dr. Yang.

DR. YANG: I would ask why? Because it seems to me like if you're going to do this, then do a CT at the beginning so you can catch the bigger denominator. If we decide that that's not clinically relevant, then what are you going to gain from looking at a subset of people that you've already prescreened with an x-ray that you know has a fracture?

DR. RAO: Any other thoughts? Any other thoughts?

Dr. Alander.

DR. ALANDER: Dr. Alander.

I would -- if they already identify with a fracture, I would not do a CT scan. It's really for those you haven't identified a problem of why they're having pain.

DR. RAO: Dr. Gilbert.

DR. GILBERT: Dr. Gilbert.

I guess it would depend on what decisions are made consequent to that and whether or not it's, you know, is the fracture still a load-bearing one, is it not a load-bearing one, does it have the chance of migration, you know; there are sort of clinical decisions, I would assume, that could be made based on different observations of that, but I'm not sure we understand what those are at this point. So I guess I don't --

DR. RAO: Dr. Lyman.

DR. GILBERT: Until and unless there is a clinical reason to do it, I'd say don't do it.

DR. RAO: Dr. Lyman.

DR. LYMAN: I'm an epidemiologist, so I like to do research. I'm just wondering if it doesn't make sense to -- if there are concerns about under-diagnosis of these fractures in this context using the x-ray methods that have been used, how about just a small pilot study of X number of patients who all receive CT to see whether or not these fractures have occurred and later making a determination about the appropriateness of CT for the postmarketing approval studies?

DR. RAO: Thank you, Dr. Lyman.

Dr. Graf.

DR. GRAF: The only thing that I could believe that that would be helpful for would be to follow those fractures out and to really see the significance of the non-unions and -- which are, you know, truly non-unions and which are not. I think that that portion would be helpful.

DR. RAO: Dr. Carrino.

DR. CARRINO: Dr. Carrino.

I think if the radiography was indeterminate or not sufficient to categorize -- characterize the fracture, then CT would be appropriate.

DR. RAO: It's my opinion, Mr. Melkerson, that the consensus of the Panel, in response to your supplemental question, is that there still continues to be the concern for radiation exposure with CT scanning on a routine basis even after diagnosis of fracture on x-ray. It's possible that some small subset could be designed to determine the utility of perhaps a low dose CT, but at this time, in general, the Panel does not feel that the utility of CT scans is very high for the diagnosis or monitoring of this group. Is that adequate?

MR. MELKERSON: Yes, thank you.

DR. RAO: Thank you.

Dr. Wyatt, we'll go on to Question 3. We're ahead of schedule right now, so we will take -- we will continue with Question 3 and take a break after Question 3.

DR. WYATT: Overall success of the Superion device as compared to the control device was evaluated based on a primary composite endpoint consisting of: clinically significant improvement in 2/3 domains of the Zurich Claudication Questionnaire, no additional surgeries at the index level, no major implant or procedure related complications, and no confounding treatments. This composite endpoint, as suggested by the FDA during review of the original IDE application, includes effectiveness measurements, safety measurements, and takes into account potential risks. Overall success for the Superion modified Intent-to-Treat cohort as compared to the X-STOP cohort was

demonstrated to be non-inferior at 24 months, per the IDE protocol reviewed and approved by the FDA.

a) Considering the patient population defined in this PMA, and the intent of the Superion device, please discuss the adequacy of the primary composite endpoint and the time point at which non-inferiority was tested.

b) Please also discuss the overall clinical success rates (in both cohorts) in the context of expected clinical success rates for commonly used treatments for the patient population defined in this study.

DR. RAO: Thank you, Dr. Wyatt.

So the question relates to the adequacy of the primary endpoint and the timeframe at 24 months, (a). And (b), the overall clinical success rates in both groups in the context of expected clinical success.

And we'll start with Dr. Gilbert this time.

DR. GILBERT: And I will advocate my non-clinician background as well when I answer this. I'm not a clinician, so it seems to me that how the patient is doing is the most important thing, and so I think these scales are appropriate. I think 24 months is appropriate. And I think I'll leave it there.

DR. RAO: Do you have a response to question (b) or part (b)?

DR. GILBERT: I defer to my clinician colleagues.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Golish, if you could speak into your mike, please?

DR. GOLISH: With respect to (a), the patient population and adequacy of the

primary composite endpoint is adequate, and the time point at 24 months is adequate.

With respect to (b), the clinical success rates in the context of expected rates, the overall clinical success of both devices in both arms seems high relative to common workaday surgical practice, in my opinion.

DR. RAO: Thank you, Dr. Golish.

Dr. Haines.

DR. HAINES: Steve Haines.

As one who doesn't generally like composite endpoints because they frequently are difficult to interpret, I like -- this one's pretty good. This is the result I'd want. I got good clinical response, I didn't have to have a reoperation, I don't have any major complications, and I didn't have to have other treatment to do well. So I think it is a pretty good composite endpoint, and 24 months is reasonable for a device like this. With respect to the clinical success rates, it's low. And thank you for getting us to the Tully article because these thresholds that are determined are -- MDICs is a minimal clinically important difference. And by allowing two of the three to be met, you could have a little bit of minimally clinically important difference in both physical function and symptom severity and not be satisfied, have a bad satisfaction score, and still that would count as success, clinical success. And when you take that and look at an overall 50% and then you worry about the comparison group, it's a pretty soft overall success rate, particularly compared to other kinds of surgery that we do.

DR. RAO: Thank you, Dr. Haines.

Dr. Alander.

DR. ALANDER: Dr. Alander.

I probably would agree that 24 months is adequate. And on (b), I would say it's also a little bit low.

DR. RAO: Thank you.

Dr. Carrino.

DR. CARRINO: John Carrino.

So, for (a), I thought the primary composite endpoint was adequate until I was a little bit enlightened by Dr. Lyman, but we'll hear his comments. And then the non-inferiority testing at 24 months would be adequate. With regards to the overall clinical success rate versus commonly used treatments in the patient population, it's the difference between efficacy and effectiveness. We expect these numbers are going to be lower in practice.

DR. RAO: Dr. Graf.

DR. GRAF: To reiterate, I believe that the endpoint and the timeframes are adequate. I also reiterate that a 50% clinical success rate is low. And in my mind, we are concluding that the product being presented is non-inferior to a product that the success rate is debated, so that's difficult to comprehend.

DR. RAO: Thank you. Any thoughts on the part -- oh, you did talk about that. Thank you, Dr. Graf.

Dr. Lyman.

DR. LYMAN: So I'm skeptical of these composite endpoints in general. It's a little bit like college ratings, and that's based on academic productivity and how good the food is in

the cafeteria and all those sorts of things. But it seems like this was pretty well vetted and you are combining safety and the patient experience. I'm also not a fan of dichotomizing the patient experience when you have a survey that's basically scored on a continuous ordinal scale and you're breaking it down to a single cut point. There's a lot of information lost, and there's a lot of loss of statistical power in doing that. And I'm not completely convinced that these were the appropriate cut points in order to determine clinical success, as I expressed earlier. That being said, it seems relatively reasonable, and it is an elegant solution to a difficult problem where we're trying to balance safety and effectiveness. As to the second point, I would defer to my clinical colleagues.

DR. RAO: Thank you very much, Dr. Lyman.

Dr. Yang.

DR. YANG: Again, I'm glad Dr. Lyman precedes me, but for (a), I'd say adequate and adequate. For (b), I'd say it's a low but soft call.

DR. RAO: Thank you, Dr. Yang.

Mr. O'Brien.

MR. O'BRIEN: Joe O'Brien.

I wish I could be as succinct as Dr. Yang. But I do struggle. Normally, I would say that a 24-month period is adequate. However, in this case, where we have an incidence of an item that we don't understand and may have long-term -- obviously it isn't long enough if we have, you know, the significant 24- to 36-month reoperation rates, then I would say that it's not enough of a period and we're looking at going postmarket of up to 5 years. So, you know, in this particular case, no, I don't think it is enough, based on what has happened

as a result of the outcomes. I do like -- I agree that I'm not a fan of composite ratings; however, I do think it was elegantly done, I agree with that, to do that. The concept of non-inferiority, though, I think goes in the face of what I firmly believe is innovation, and I struggle with seeing how that really applies to innovation. But that's me, I guess.

DR. RAO: Could you expand on that just a little bit?

MR. O'BRIEN: Well, in spine surgery, historically -- and we'll continue, and from a patient perspective, we look for innovation. It is essential to have innovation. If you go from procedures to today, what's happened with pedicle screws, for example, that's necessary to do that. And for that perspective, it is absolutely essential to do things like Superion, et cetera, et cetera. I think that's absolutely there, to do that. However, that isn't always successful, and it is important to be able to step back. If we're looking at just non-inferiority, comparing what's there -- I understand the control, I understand why it was done; I'm not questioning that. But in terms of what we end up in the end of the day, it becomes a very low benchmark in terms of what's really there. We're looking for something that's better, not that's non-inferior, from a patient perspective. That's my point on that.

To 2, you know, I answered 2 in thinking in terms of responding to a patient's question. It's a 50-50 chance, you know. You know, in terms of the success rate, it's 50%. That's not a very high chance for someone, so that, you know, when you put it in that perspective, it becomes hard to accept that level. And to the point that was made earlier in the public comment, it is true that when you look at most new innovative procedures, that if you follow them 10 years later, we're getting much more reoperation rates, and it's much

higher than what was originally reported by the champions of that, so, you know, while today we have a reoperation rate of X, it's going to be X-plus 10 years from now. That just happens to recur, so you know, to that -- again, when I look at it, it's not -- I was surprised by the low rate.

DR. RAO: Thank you, Mr. O'Brien.

MR. O'BRIEN: Short answer.

DR. RAO: Thank you.

Dr. Trier.

DR. TRIER: Yes, Dr. Trier speaking.

For (a), I have concurrence with the rest of the Panel or most of the Panel members with adequate/adequate. For letter (b), I did want to speak to that. You know, when you look at the success rate based on the composite clinical success criteria, it is a very complex criteria. There are several elements, four elements, that are all bundled together as one single hypothesis test. The comfort I have is the fact that when you look at each of the individual criteria, they all show a success of over 80% or over on each of those specific criteria individually. And so when I look at the composite, the single hypothesis based on CCS, I recognize that it's very complex, that you have to be each of those to be considered to be a success. But when you disentangle all of those and you look at them individually, they had 80% or greater success on each of them as individual elements. So I would say that the success rate is what it is, but I have a comfort level that on each of those criteria, there was a great amount of success demonstrated in the data.

DR. RAO: Thank you, Dr. Trier.

Mr. Melkerson, with regard to Question No. 3a, the Panel generally feels that the primary composite endpoint, while not a generally welcome system, was adequate and the time point at which non-inferiority was tested was adequate. There is some concern about the use of two out of three groups in the ZCQ and to whether leaving out the patient satisfaction or the patient experience criteria bucket from the ZCQ may lead to a less-than-full evaluation of the product.

Is that adequate for part (a)?

MR. MELKERSON: Yes, thank you.

DR. RAO: For part (b), Mr. Melkerson, the Panel generally feels that the overall clinical success rates in the study were soft or weak and that they may be further compromised by comparison with a product that does not have generally outstanding clinical results, and that we will need a longer time period to fully understand whether the product is a valuable addition to the armamentarium of the spine surgeon.

Mr. Melkerson, is that adequate?

MR. MELKERSON: Yes. Thank you for your input.

DR. RAO: Thank you. It is now 2:41. We will take a 15-minute break. So I would ask the Panel members to go to the table and check your travel arrangements, but we will meet at exactly 3 o'clock back in this room and continue with Question No. 4. Thank you, all.

(Off the record at 2:41 p.m.)

(On the record at 3:00 p.m.)

DR. RAO: If we can have the Panel members sit down again, and if we could have the FDA ready at the podium, please. If someone could close the door, and we will get

started. I believe we have all our Panel members.

Dr. Wyatt, if you could go ahead with Question No. 4, please. Is it Question 4 now? Yes.

DR. WYATT: Yes, Question 4. And it's a bit of a long one, so I'll try and work through it a piece at a time.

In May of 2008, the Agency approved the Superion IDE clinical trial using a PMA approved device, the X-STOP, as the control. Subsequently, as described above, overall success for the Superion as compared to the X-STOP was demonstrated to be non-inferior at 24 months. The Agency is aware of literature which has been published on interspinous process spacer devices including randomized controlled clinical trials, which suggest that decompression alone (i.e., the "gold standard" to treat lumbar spinal stenosis) results in comparable effectiveness outcomes compared to treatment with an interspinous process device alone, although use of an interspinous process device is associated with a higher reoperation rate. In addition, the Agency is aware of recent literature which suggests patients with degenerative spondylolisthesis should be considered as a distinct sub-population of spinal stenosis patients, and the use of interspinous process devices to treat patients with degenerative spondylolisthesis is controversial. Please comment on whether the literature referenced above is a fair representation of your current understanding of treatments available for this patient population and whether or not the findings are relevant to the device under discussion today. If so, please discuss the impact, if any, this literature has on the interpretation of the results of the Superion study (e.g., study design, study endpoints, determination of benefit-risk, device labeling, etc.). Please note that your

feedback may also be useful to the clinical trial design of future interspinous process spacers.

DR. RAO: Thank you very much, Dr. Wyatt.

I think we'll start with Dr. Carrino this time around.

DR. CARRINO: Okay, thanks.

So, working as a radiologist, I don't have the same treatment perspective, but I think that understanding the nature of spinal stenosis from the imaging side and working closely with surgeons, that it is a progressive disease, and I think it's reasonable to look at intermediate types of treatments that are not meant to be cures but are meant to be bridges and meant to be helpful for whatever period of time that they may clinically think is useful: 2, 3, or 5 years. And that's my perspective, and I'm interested to hear what my surgical colleagues will state.

DR. RAO: I'm just going to pin you down, if you don't mind, Dr. Carrino.

DR. CARRINO: Sure.

DR. RAO: And just explain that answer just a little bit more with respect to the specific question being asked.

DR. CARRINO: Yeah, I'm still trying to understand the question, but --

(Laughter.)

DR. CARRINO: -- if we could pin down the question, I'm happy to pin down my answer.

(Laughter.)

DR. RAO: I guess there's two parts.

DR. CARRINO: Yeah.

DR. RAO: They want to basically know whether the literature referenced above is a fair sample of the body of literature on these particular issues, number one. And, number two, whether the endpoints represented in that literature is generally consistent with the endpoints for future interspinous process spacer device studies.

DR. CARRINO: Okay. But that's --

DR. RAO: Is that a fair summarization?

DR. WYATT: That's a fair assumption. I would also add the point that, to kind of paraphrase the question, is -- the literature demonstrates comparable effectiveness between interspinous process devices and treatment procedures which do not involve a device. And so moving forward with that information, does that affect the benefit-risk profile of the device we are looking at here? And then please note, you know, is there information that could be gleaned from those literature to inform future sort of device design, device trial design?

DR. RAO: Thank you, Dr. Wyatt.

DR. CARRINO: Okay. So this is the literature that I don't necessarily follow and did not have an opportunity to review this paper, so I don't have an opinion on the paper and don't have any knowledge about the treatment outcomes. I do think that probably there could be some information gleaned for future trial designs, but I don't have any specific information.

DR. RAO: Dr. Alander.

DR. ALANDER: Dr. Alander.

I think that the literature that's listed is a part, but it's not the whole, and I would not refer only to that, so I don't think it's necessarily totally representative. With regards to the spondylolisthesis, should we go into that? Utilizing that as a distinct subpopulation, I think that it does have to be a distinct subpopulation. And that's mainly because of the disc height, whether how stiff they are in their vertebral bodies, bony encroachment versus soft tissue encroachment.

DR. RAO: Thank you, Dr. Alander.

Dr. Haines.

DR. HAINES: Steve Haines.

As was mentioned, it's a subset of the literature, but it's a reasonable representation of what's out there, and certainly spondylolisthesis suggests that something more is going on with those patients than with those who don't have it or don't have it yet and need to be looked at separately. I think that there's an implied comparison to decompressive -- to surgical decompression, and I think that's a false comparison. I think that it will be very difficult to interpret direct comparison trials because I think this is a bridge therapy. It's very likely to end up as a way to delay decompressive surgery in many people and perhaps forever in some. But they are very different procedures with different mechanisms of action, different expected longevity, and I think that direct comparison is not a very good idea.

DR. RAO: Thank you, Dr. Haines.

Dr. Golish.

DR. GOLISH: With respect to the literature listed here, I think it's representative and

germane, although a subset, as Dr. Alander mentioned. With respect to the issue of spondylolisthesis, I agree that it is a different clinical entity, but it is typical in regulatory trials and academic trials to include Grade 1 stable spondylolisthesis within stenosis with the warts attendant in that, so I think that that is adequate. But, more importantly, with respect to the overall trial design and are these issues germane, especially the last portion about "useful to the clinical trial design of future interspinous process spacers," I guess I would say that we've heard from the Sponsor a number of times that they took the opportunity to meet with FDA, the meeting of the minds, and try to agree on the trial structure and design, and I applaud them for doing that.

You know, all the panelists understand that the pre-IDE process is nonbinding, but it behooves you to do that. We hear that you have, so I'm respectful of that. But that said, I do feel like the non-superiority trial as a two-arm with respect to the particular device and it's -- everything attendant with that is challenged as opposed to, as you suggested, a non-inferiority study relative to microsurgical decompression or inferiority study relative to something else.

DR. RAO: Thank you, Dr. Golish.

Dr. Gilbert.

DR. GILBERT: Yeah, I have really no opinion about the subpopulation of the spondylolisthesis group. I would comment on the papers. I think these particular papers cited tried to make the comparison of the decompression surgery versus the interspinous device and found no difference in outcome between them and I think made some comments about evidence-based medicine. You need to be making improvements

compared to the gold standard; otherwise you just continue to do the gold standard. I heard here today good reasons, I think, for why you would do an intermediate procedure, that you still preserve the option of decompressive surgery later on, so I think that's something that's important to note here.

And in terms of the impact of the literature on the study design, study endpoints, I think the literature raised some -- maybe more clearly, the risks or the presence of fracture of the spinous structure and that that risk needs to be better understood and mitigated. And so I think, going forward, the identification of this as a risk is one thing, noting what the severity of the consequence of that risk is and the incidence rate is important.

And then what are methods beyond what the Sponsor has already said could be brought to bear to mitigate the risk. And I think there are additional things then, labeling and training that the Sponsors could do to try to address that risk. I am curious; earlier FDA said that all preclinical testing was complete and there was no need for anything additional, and I'm not suggesting that they have to go back to doing that, but it seems to me better understanding of what results in a spinous fracture is needed for biomechanics studies and approaches for design of the device that could mitigate against that risk need to be considered.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Graf.

DR. GRAF: I do agree with the almost statement in the question itself, that the decompression alone would be considered a gold standard. And the literature itself does demonstrate a high long-term complication rate. I did a literature review myself in

preparation for this session, showing that, for instance, Bowers had a 38% complication rate with 85% of the patients undergoing additional surgery; Tuschel in *Spine* of 2013 having a 30.4% revision rate; and Verhoof in the *European Spine Journal* having a 58% failure rate. Now, I know that's a different product than --

DR. RAO: This is with which intervention?

DR. GRAF: This is with interspinous devices as a whole, not inclusive of this device because it's obviously a subject today. The North American Spine Society clinical guidelines all note, which I think is true, that there is insufficient evidence to weigh in on this. I do agree with a direct comparison. It would be interesting to see a direct comparison of this type of implant compared to, as stated, the gold standard of a decompression, but in my mind, that would have to exclude spondylolisthesis because that wouldn't be a fair comparison. So I do agree with the spondylolisthesis subset, you know, being a distinct subset.

DR. RAO: Thank you, Dr. Graf.

Dr. Lyman.

DR. LYMAN: So, as we heard earlier, I guess -- and we didn't have verification of this from the FDA or anyone else, but the Panel originally did not want to approve X-STOP, but FDA approved it anyway. We heard that during the public comments. So I guess, in my mind, I'm like well, if you're taking something that was a controversial device from the beginning and using that as the comparison group, you're setting a very low bar for what would be clinically, you know, effective. And then on top of that, you're only looking at non-inferiority; you're not looking for an improvement. And so that just seems -- like, I'm

not sure that I would go down that path again if another one of these devices was coming to market. But on the other hand, and I'm not an engineer and maybe we can get a little clarification; it seems to me like maybe this device is a step forward over the previous device because there was no migration or dislodgement in the new device cohort. So it may be that the design is an improvement over the previous designed device or approved device, but is it enough? Is it a big enough step forward given the risk of revision surgery, the risk of these fractures? I just don't -- I don't have an answer to that, but it's just things that I've been thinking about as we've been talking today.

I don't have an opinion of the spondylolisthesis; I'd leave that to my clinical colleagues. I do wonder if maybe the path, in the future, for these studies might be a three-arm trial where surgical decompression is a third arm allowing for the gold standard to be included in the assessment. And, you know, I'm also thinking that if -- I'm hearing from the clinicians, they consider this a bridge procedure. So, if we're able to save some percentage of patients from needing a more invasive procedure down the road, then a high failure rate may be okay because you are preventing those bigger operations later on.

I think that's everything I had to say.

DR. RAO: Thank you, Dr. Lyman.

Dr. Yang.

DR. YANG: So, with regard to whether or not this is a fair presentation, I'd have to agree with Dr. Haines on this one. I think you're comparing apples and oranges on many different levels, and not the least of which is one, as you said and as Dr. Haines said, you know, this is probably going to turn out to be some sort of bridging device, and if so, you're

comparing that to a procedure that's supposed to have long-lasting effects. So I don't know that that's a fair representation. With regard to spondylolisthesis as a separate group, I think when you don't know what the mechanism is, you have to be very careful about lumping things together, and even if, you know, in general a large number of these studies lump Grade 1 with, you know, no spondylolisthesis, I think when you have no idea what is really happening, then you probably do need to hold those separate.

DR. RAO: Thank you, Dr. Yang.

Mr. O'Brien.

MR. O'BRIEN: From a patient perspective, very rarely does a patient ask for X-STOP versus Superion; that's usually not what's on their mind. So, if we're going to be patient centered, what's more important? They are familiar with decompression or decompression with fusion or interspinous process, so to me it seems like the design, it's more valuable, from a patient perspective, to have those questions answered relative to that. To the issue of bridging, it really hasn't been identified that that's what it is. I brought up that terminology, but that's really not what I saw in anything that I've read that that's what the intent is. As I expressed or tried to express when I look at this, this is a patient population, particularly when we get into some of the complications, at 67 years of age, that's there. So, if it's going to be 2, 3, 4, 5 years, we now have a 70-plus population that may need now that more aggressive surgery that they may have had and avoided in the first place.

From a patient perspective, I've had four surgeries for my spine. And when you talk to a patient, yes, there are considerations for complications for a particular surgery and the severity of that surgery. However, the mindset of saying I'm going to have to go back in

3 years or 5 years or whatever is very significant to them, from a psychological perspective and from an emotional perspective, and it may be from a physical perspective, because you have more comorbidities now that you go forward. So, to that extent, I think it's very important to compare a study design that says this, you know, interspinous process versus whatever the case may be, as opposed to within a particular device in terms of the design for that. And to me, that's what the literature -- I'm no expert on the literature, but reading the literature and knowing -- and those global issues that patients are dealing with at this population, that's more of a concern.

DR. RAO: Thank you, Mr. O'Brien.

Dr. Trier.

DR. TRIER: Yes, this is Dr. Trier.

With regards to the literature that has been cited by FDA, I think the literature is interesting. I think it's literature that should be taken into consideration with future study design. I don't think it should be the deciding factor about the study design. With regards to the spondy subgroup, I would defer to the clinicians about how to handle that.

DR. RAO: Thank you, Dr. Trier.

Mr. Melkerson, with regards to Question 4, the Panel generally believes that the use or the determination as to which subgroup should be used for comparison will, to a large degree, depend upon what the proposed intent of the device is. If the manufacturer states that this is a curative treatment for spinal stenosis, then it might be appropriate to use a comparator group which includes the traditional gold standard, which is spinal decompression. But if this is being looked upon and proposed to our patients as more of a

temporizing measure, then it may be reasonable to use a comparator group for similar interspinous process device. Further, the literature cited in Question 4 is part of the overall body of literature that has been published on interspinous process distraction devices, and there are several other papers that should be taken into consideration to get a better sense of the entirety of the science on this issue.

As far as the degenerative spondylolisthesis group goes, again, if the intent of the device is being promoted as a bridging or temporizing measure, it may be reasonable to include the degenerative spondylolisthesis group. But if the intent of the device as stated, and as our patients are made aware, is of a curative nature, then inclusion of the degenerative spondylolisthesis group would likely be inappropriate.

I think that covers the question, Dr. Wyatt. Is that -- did I cover all aspects of your question?

DR. WYATT: Yes, that's satisfactory. Thank you.

DR. RAO: Mr. Melkerson, is that response satisfactory?

MR. MELKERSON: Actually, I'd like you to put up -- Zane, if you could put up the indication for use and then just ask the question: Based on what the indication for use proposed in the PMA is, does that change anybody's answer? Because that is what we're considering. Instead of guessing is it a bridging device or not, what is the actual indication for use actually proposed by the Sponsor? And that's the context in which this question was asked.

(Pause.)

DR. RAO: I'm going to go around the table real quick again, and Dr. Carrino, if you

have any thoughts based on these indications for use, keeping in mind Question 4. So the issues we have to discuss are the literature, the body of literature, the utility of a comparator group of open decompression versus another interspinous process device. I think those were the two broad areas, correct? So the comparator group and the literature. And comparator group seems the more important -- and the degenerative spondylolisthesis.

DR. CARRINO: The information we're looking for is whether these indications are still --

DR. RAO: Whether these indications, as stated, would be appropriate for this device, because these are the indications that our patients are going to read or understand. So do they need more clarity in the indications?

Is that your question, Mr. Melkerson?

MR. MELKERSON: It's not just the patients; it's also the users, the surgeons themselves. These are the indications that you're describing, so is it or is it not a bridging device is going to come from this language.

DR. RAO: Thank you, Mr. Melkerson.

Dr. Carrino.

DR. CARRINO: Yeah, I think the indications as stated are suitable. How it's used in practice depends on what happens with the person. If this person has moderate stenosis and these symptoms and this treatment or some other treatment is applied and they do well, then it may be fine for their clinical course. We're not able to always predict what's going to happen to them. So I think the way the indications for use as stated are fine.

DR. RAO: I guess the question Mr. Melkerson may be trying to get to is that word "treat" in the first line, because if it is, what exactly does "treat" mean? Is it curative or is it a bridging type of temporizing measure?

Would that be a fair interpretation of your question, Mr. Melkerson?

MR. MELKERSON: I just wanted to make sure that we're taking it in context of what is being proposed by the Sponsor because the bridging language was brought up in a discussion point, not actually what was proposed by the Sponsor.

DR. RAO: So --

DR. CARRINO: I'm not familiar with the way indications are usually stated, but is "curative" typically included in an indication?

DR. RAO: I guess that -- I'm going to leave that to you to determine --

DR. CARRINO: Yeah.

DR. RAO: -- whether how the physician and the patient is going to see the word "treat."

DR. CARRINO: Yeah.

DR. RAO: And whether these indications, as stated by the Sponsor, will demand a different comparator group, will allow the use of degenerative spondylolisthesis in this group.

DR. CARRINO: I think with all of those, it's still suitable.

DR. RAO: Thank you, Dr. Carrino.

Dr. Alander.

DR. ALANDER: Dr. Alander.

I think it's still pretty ambiguous. I'm not certain that it tells us exactly what we're doing here, so I'd stick with my original comments.

DR. RAO: Could you just restate those comments with -- now that we have these indications up?

DR. ALANDER: So I think that the literature, as stated, is a subset. I don't think it's inclusive. I do think that spondylolisthesis should be a separate subset or separate study.

DR. RAO: Dr. Haines.

DR. HAINES: Steve Haines.

Well, these indications are silent on the expected duration of benefit. And I think there's a reasonable analogy to other conditions where we have alternative treatments, one intended to be curative, one that manages the situation and may hold a patient for a very long time but may not. Treatment of benign tumors, either surgically or with radio surgery, for example. We deal with this all the time. Different patients with exactly the same appearance on their images will make different decisions. And so I don't think that -- I think that the silence on the indication statement is part of the immaturity of this concept, that it hasn't been -- we don't know what the duration of benefit is. The study was not designed to find that out, the proposed study is not designed to find that out, and therefore it's very difficult to change the comments that have already been made. The literature is there; spondylolisthesis is different than not having spondylolisthesis, and it's not clear that the goal or result of treating moderate lumbar spinal stenosis with surgical decompression is the same as using an interspinous spacer.

DR. RAO: Thank you, Dr. Haines.

Dr. Golish.

DR. GOLISH: My answers to Question 4 haven't changed. I think the indications for use listed here are clear, in summary. With respect to the literature listed, it's germane but not comprehensive. With respect to spondylolisthesis, I agree it's a distinct clinical entity, but it's also common in regulatory trials and in academic trials to include it, Grade 1 stable within the stenosis category. And then with respect to the third point, I've already stated that I think the trial design, by its nature, has challenges with respect to its intended purpose.

DR. RAO: Thank you, Dr. Golish.

Dr. Gilbert.

DR. GILBERT: As I think back on the discussion, I think part of the issue here is that the Sponsor came forward with the concept that you could do this procedure; if it fails, then you could go to a full decompression, and I think the term was a "virgin decompression" could be performed, which I think then led us sort of down this road of a bridging device. But I don't think that was the intent. I think that was a pointing out of a potential benefit, if you will, and so I don't see this as being a bridging device. This may last the life of the patient, and I don't think there should be anything that says it's a bridging device because then you're putting in the perception that if you do this, no matter what, you're going to have it out and something else done. And so I don't think changing the indications for use are merited. And then I've spoken to -- I have no opinion on the spondylolisthesis. I think the literature does represent the state of understanding of the relationship between interspinous devices and decompression. It's not the complete literature, I agree with that.

And then I think there are impacts on subsequent study design and evaluation of this device and others that may come.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Graf.

DR. GRAF: And continuing with that thought, that's what I brought up earlier, in comparison of this device to a laminectomy or a decompression, if you will. It's difficult to compare those two because you're comparing, what we just stated prior, is the "gold standard" procedure. Yes, that gold standard procedure can still be performed after this device. It's not fair, though, to compare that initial gold standard procedure to a revision, a decompression, which is a whole different animal. As far as the indications for use, I do agree with the indications for use as they're stated.

DR. RAO: Thank you, Dr. Graf.

Dr. Lyman.

DR. LYMAN: So, in listening to the discussion, I went back to the Sponsor's slides, and Slide No. 9 was their spectrum of this condition and the potential treatment algorithms, and I didn't hear any of the clinicians on the Panel challenge these assertions. So, if that's the framework, then laminectomy and these devices do overlap in their indications, so I do think it would be appropriate to use decompression as a comparison group in future studies with appropriate indications and inclusion/exclusion criteria around the study. You know, you have to have clinical equipoise obviously, so the surgeons enrolling patients in the trial would have to agree that they would be willing to do either/or in any patients that met those inclusion criteria.

DR. RAO: So I don't have the wording, but I think -- so you are recommending that the comparator group be a decompression then? An open direct decompression?

DR. LYMAN: Well, to get back to my previous comments, I thought that we were setting a very low bar by comparing to a controversial device that's already approved, and therefore why wouldn't we compare to the gold standard, so a three-arm trial may be a way around that.

DR. RAO: Okay. Thank you very much, Dr. Lyman.

Dr. Yang.

DR. YANG: I think we have to be careful about regulating a device versus regulating the practice of medicine, given that there's no data, et cetera, at this immature stage and all these interspinous processes, like Dr. Haines says, there's no duration of treatment, et cetera, so I do think that at this point the indications for use, the way it's stated, is probably reasonable because you can't regulate how someone is going to use that. That's regulating the practice of medicine. So, if that's the case, then that brings in that whole bridging thing because that's how that individual surgeon chose to use it in the context of page 9 there, or slide 9. So, as far as whether it changes my comments from previously about this being a comparator and all of that, I still think that it's probably not a totally fair comparison to go with laminectomy, even though it overlaps a little bit, because we don't know where this comes into play. It may be more fair to compare it to, you know, another interspinous device. And as far as spondylolisthesis, the question, as I read it, is for future studies, not questioning the indications as they wrote it here. I think if the question is are the indications okay, I would say the indications are okay to my -- you know, at this point in my

assessment, but if you're going to go forward with some future studies, I think not knowing the mechanism means you probably want to take it apart as a separate group.

DR. RAO: Thank you, Dr. Yang.

Mr. O'Brien.

MR. O'BRIEN: In terms of the indications for use, my previous use of the term "bridge" was not referring to their risk assessment or benefit assessment by being able to still do other procedures that are there; it was in context to the outcomes relative to the amount of reoperations. And, in particular, you're looking at Month 24 to 36, where we now had a spike of reoperations that were required and up to 25% of the patient population, so it begged that question that with the incidence of fractures being high and with the incidence of reoperations being high to begin with, and with this trend in the last 12 months, are we therefore telling patients is this a bridging mechanism with the other nature that's been described of this condition to begin with?

That was my reference to the bridging, which I think is important, one, for the clinicians to understand, if that's what the results of the study indicate. And I don't know if we have the final answer yet, but leaving that and looking at the trending, I'm saying okay, is that -- and with that, it's not only important for -- if that's the case, then I think that any literature or any patient education or any discussion between the clinician and the patient has to say that we have a very high rate of "potentially you'll be back." I think that's an important message that has to be there.

DR. RAO: Dr. Trier.

DR. TRIER: Listening to the comments from the clinicians here and then looking at

the indications for use, you know, using the word "to treat skeletally mature" patients, and then the rest of the indications for use does not preclude whether or not it's expected to be a shorter duration or a longer duration. I have no concerns about the indications for use.

DR. RAO: Thank you, Dr. Trier.

I think, Mr. Melkerson, in response to your request for clarifications, the Panel generally feels that there is some lack of clarity as to the duration of efficacy of these interspinous process devices. As a result, it is unclear or it is equally acceptable, perhaps, to use both other interspinous process devices as well as open or decompression, direct decompression as comparator groups for the evaluation of an interspinous process device. At the same time, if it was being compared to an open decompression, then perhaps the inclusion of the degenerative spondylolisthesis subgroup may not be entirely appropriate in that particular study. The literature is appropriate as cited, but there is a vast body of literature that refers to both open decompression, other interspinous process devices that should be used in totality to assess the body of science on this issue. I hope that clarification is adequate.

MR. MELKERSON: Very much so. Thank you.

DR. RAO: Thank you very much, Mr. Melkerson.

The Panel will now move to Question No. 5. Dr. Wyatt, if you could read that.

DR. WYATT: Just prior to Question No. 5, I'd like to remind the Panel that the discussion of a post-approval study prior to FDA determination of product approvability should not be interpreted to mean that the FDA is suggesting that the product is safe and effective. The plan to conduct a post-approval study does not decrease the threshold of

evidence required by the FDA for product approval. The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk-benefit balance.

Question No. 5: If the Superion device is deemed approvable by the FDA, the sponsor has proposed a post-approval study to continue following the IDE subjects for up to 5 years, as well as an additional "actual conditions of use" post-approval study which would enroll new subjects. Please discuss the adequacy of the sponsor's proposed post-approval study plans for the evaluation of the safety and effectiveness of the Superion device in the postmarket setting. In your discussion, please specifically address the following:

a) The proposed new cohort post-approval study is powered to demonstrate that Superion performance is not clinically inferior in the new Superion cohort as compared to the pivotal IDE Superion cohort based upon a comparison of the primary endpoint at 24 months. The proposed secondary objective of the new cohort study is to compare clinical outcomes in subjects implanted with the Superion device to clinical outcomes in subjects treated with surgical decompression at 24 months postoperatively. Please discuss the clinical importance of these two objectives, and discuss the most clinically relevant primary objective of the new cohort post-approval study.

Would you like to go to the other one or answer this one first?

DR. RAO: Why don't we do this one first? Let's just go around the table in different order this time. Why don't I start with you, Dr. Yang, and come around. So, if you could give us your response to part (a) of Question 5.

DR. YANG: Okay. So, as to whether or not the proposed primary -- I'm restating this because I'm just thinking it through as I'm doing this. But it's a comparator for a non-inferior study at 24 months. I think given that, at this point, it's -- as we already hashed through in the last one, the comparator group can be both, you know, laminectomy and other interspinous devices. The only comment I would make there is if this is a post-approval study, perhaps we should go out to more timing so that we can start to address the duration of effect, et cetera, rather than just 24 months. And the secondary objective, again, I think we just hashed through that. It really depends on, you know, what we find out about the length of duration of effect. So I can't comment any further, I don't think.

DR. WYATT: Dr. Rao.

DR. RAO: Go ahead.

DR. WYATT: May I make a clarifying point?

DR. RAO: Please do, yeah.

DR. WYATT: To summarize this question, the proposed primary objective is non-inferiority of the postmarket cohort to the IDE cohort, and the secondary objective is the postmarket cohort to decompression. The intent of the question is to ask, should -- is that order, primary and secondary, appropriate?

DR. RAO: It would be two different studies, correct? It's two different studies. One is comparing just the Superion group, is that correct or --

DR. WYATT: Yes, that's correct.

DR. RAO: Two different studies?

DR. WYATT: But the question is, which should be the primary versus the secondary

objectives?

DR. RAO: Okay, okay. Thank you very much.

Dr. Yang, do you have any additional thoughts?

DR. YANG: The only additional thought I have is without understanding the duration of effect, I think you can't tell what's your primary and what's your secondary. Because if the primary is comparing to the previous group and the secondary is comparing to laminectomy and you don't know how long this effect lasts, then you don't know which group to compare to.

DR. RAO: Thank you, Dr. Yang.

Dr. Lyman.

Hold on just a second, Dr. Lyman, if you don't mind. I'm just going to go to Dr. Alander for a second.

DR. ALANDER: I just want to clarify. So this study, the follow-up study at 5 years? Okay. Or not? I mean, you're going to --

(Off microphone response.)

DR. WYATT: All right. So there are two proposed postmarket studies. One is a follow-up up to 5 years of the IDE cohort. The second is a new enrollment study. That new enrollment study has these two objectives. So the question asked here is, what should be the order of those objectives?

DR. RAO: I guess we already have data to 36 months, so they would just extend that to the 60-month stamp. I think we are at Dr. Lyman, so I'll go back -- and just, I'm going to interject for just a second. Dr. Alander, I'm going to begin the next subpart question with

you, so I'm just giving you a little warning here.

I'll go to Dr. Lyman now for part (a), for your response to part (a), please.

DR. LYMAN: So my impression here -- so I thank you for the clarification about what studies we're talking about. So, obviously, I think it's completely appropriate to go out to 5 years with, you know, the original IDE cohort. But I worry a little bit about the new -- comparing this non-inferiority study of the investigational cohort being compared to the post-approval cohort. That seems to me -- in one way you're talking about probably expanded indications, probably non-experienced surgeons. They're actually almost setting themselves up to fail in the sense that you would expect the clinical effectiveness is going to be reduced compared to the efficacy that was determined during the definitive trial. So I would actually recommend that these two be flipped, that the decompression be the primary analysis and that's how the study is powered, and then a secondary analysis is whether or not they're able to maintain the clinical effectiveness, the efficacy, found in the IDE with the postmarket approval study.

DR. RAO: Thank you, Dr. Lyman.

Dr. Graf, please.

DR. GRAF: That was my thought exactly. This brings into question of what the "actual conditions of use" is defined as. Is that implying that patients that aren't technically fitting into the FDA approval for this device are going to be somehow included in this study? I don't know. In my mind, the primary consideration would be study number two, as we've gone over directly comparing this to the gold standard laminectomy, decompression.

DR. RAO: Thank you, Dr. Graf.

Dr. Gilbert.

MR. MELKERSON: Dr. Rao.

DR. RAO: Yes. Yes, Mr. Melkerson.

MR. MELKERSON: Just to clarify that last question. The post-approval study would be for the same indications for which a PMA is approved. A new cohort would be general experience for the indication that was approved. It's not an all-comers for all indications.

DR. RAO: I'm just curious why you felt it was important to point that out, because I may be missing something.

MR. MELKERSON: Well, your question said for indications that weren't part of the approval and the conditions of approval are limited to the same indications. The purpose of a new cohort study is how does this device function in the hands of somebody who is not trained or part of a research center.

DR. RAO: Thank you, Mr. Melkerson.

Dr. Gilbert.

DR. GILBERT: I completely agree with Dr. Lyman. I think the comparison of non-inferiority to decompression with the secondary objective is a broader application of this with a broader population of surgeons should be a secondary part of the study.

DR. RAO: Thank you, Dr. Gilbert.

Dr. Golish.

DR. GOLISH: Further clarifying questions. In study number 2, the new enrollment study, is the decompression arm newly enrolled or historical?

DR. WYATT: Can you please repeat that?

DR. GOLISH: Okay.

DR. RAO: It would be a new arm because there is no historical decompression arm.

DR. GOLISH: Okay. Not historical relative to the trial. So, in study number 2, the new enrollment study, is the decompression arm a new enrollment decompression arm, or is it relative to historical evidence in the literature in terms of the effect size?

DR. WYATT: It would be a new --

DR. GOLISH: Okay. So an observational study now or a randomized trial?

DR. WYATT: Randomized trial.

DR. GOLISH: Okay. So you're proposing a second randomized trial or the Sponsor has proposed, and you're asking what should be the primary outcome of that, this new enrollment trial?

DR. WYATT: Correct. Should the primary objective be comparison to decompression or comparison to the IDE cohort?

DR. GOLISH: So now that's clear to me. In my opinion, it should be comparison to the decompression as a primary and comparison to the outcome from the IDE trial for the device as secondary.

DR. RAO: Thank you, Dr. Golish.

Dr. Haines.

DR. HAINES: Steve Haines.

Okay, so everybody's been really nice so far. This doesn't make any sense --

(Laughter.)

DR. HAINES: -- the way it's proposed. What you're proposing is a randomized trial in

which the primary goal is to do a historical comparison of one arm of the randomization to a non-inferiority trial that we're talking about today. And then as a secondary look, we'll look at all the randomized people and do that -- it doesn't make any sense. So, if we want to follow a cohort of patients under the conditions of actual use, having that cohort be one arm of a randomized trial is not conditions of actual use. All of those surgeons will have been trained up to a standard for a randomized trial. We know patients in randomized trials generally do better in general health because they're getting a lot of attention. They may do worse in the actual measured outcome because they're getting more attention to doing that. It's not -- it doesn't approximate actual use.

So, if the purpose of the historical comparison is to figure out if putting this out in practice leads to a different outcome, you got to do it in a completely different way. The randomized comparison, there's an important question to be answered in the randomized comparison, but it's a very complicated question that can't be answered in 24 months. The duration -- if we believe the 36-months data that we're shown here today, X-STOP is starting to really fail between 24 and 36 months. So using a 24-month window doesn't make any -- it just protects you from having to observe the failure of the device in the future, if there might be. So it has to be longer.

The surgical decompression is intended to eliminate the disease at that level. Yes, there is a recurrence rate and so on, but it's a reasonably long-lived procedure. Any stopping point in the observation introduces a bias against the surgical decompression because every year you go without having to do anything else is an additional benefit. You've paid the price all up front and you're getting the benefit every year you go, so any

place you cut it off puts some bias into it. Where that number is, I don't know, 5, 6, 7 years, but it's a long study; it's not a 2-year study. And, finally, when you look at the risk-benefit and the cost-benefit, you've got -- in those patients who first had an interspinous device and then went on to have a surgical decompression, the cost of all of that and all the risk has to go into the comparison. And so it's a much more complicated study than has been proposed here.

DR. RAO: Thank you, Dr. Haines.

Dr. Alander.

DR. ALANDER: How do I follow up on that?

(Laughter.)

DR. ALANDER: I think it does -- the cohort certainly has to continue out a lot longer, and I do think that comparison between the implant and decompression has to be done as a separate study, long-term.

DR. RAO: Dr. Carrino.

DR. CARRINO: I want to start off saying I'm so glad that I'm the last one for this question.

DR. RAO: You're not the last one.

(Laughter.)

DR. CARRINO: I'm so glad that almost everybody else went before me on this question. I think there was a lot of good discussion, and it's very clear to me now that a new trial should have decompression as one of the arms for a randomized control trial and that should be the primary endpoint.

DR. RAO: Thank you, Dr. Carrino.

Dr. Trier.

DR. TRIER: Yes, Dr. Trier here.

Having had this experience firsthand, as the Industry Representative, when I look at this question and listen to the discussion today, really the question is asking a very simple -- I mean, it's a very simple question. It's how do you power the study? Do you power the study off of the primary endpoint as it's called out here or the primary objective, or do you power it off the secondary objective? That's really what you're asking. So it's not a matter of do you follow these patients or do a new enrollment study and follow these patients whether it's 24 months or 36 months or whatever that magic time point is, or do you add another arm, which is decompression. You're really talking about how do you calculate the sample size, what's the primary hypothesis.

So, you know, as FDA historically has done with post-approval studies like this, they have been actual conditions of use. In other words, it comes from the philosophy -- and this came right from the Agency in my personal experience -- they want to understand if, in the hands of the general surgeon, you know, after this device is on the market, you know, will this device, in the hands of surgeons out there, not part of the IDE, be able to perform as well or at least not inferior to what it did in the IDE. So, in a sense, I'm not sure it really matters which is the primary and which is the secondary as long as both of them are part of the data collection processes for the study. And, from my perspective, I think that really to a large extent, it should be negotiated between the company and FDA to make a determination about what is primary and what is secondary.

DR. RAO: Thank you, Dr. Trier.

Mr. O'Brien.

MR. O'BRIEN: Joe O'Brien.

I'm actually glad to get this question because I can really, with this one, have a very positive attitude, and I really do applaud the Sponsor for the proposal for these postmarket studies. I think all of the questions are important, even to answer what we're supposed to answer today, I think they're important. I think continuing to the 5 years is absolutely essential, as far as I see, and really to get the question answered. I think the two proposed -- while I'm not quite sure I think I got all your points and I agree with Dr. Trier, except I would -- my sense is the more important question is the one to decompression. But the other one is also important because every panel I sit here, that's always the relative question is what happens when it gets to the hands -- with the cowboys and the cowboys hurt people.

And I -- sorry for that phrase, but when it gets outside, beyond, in rural areas or wherever the case may be, that's where we see patients that really are getting hurt, and I think it's important to understand that and somehow make sure we protect with that, so I think it's equally an important question to answer. But it does seem to me, and I would agree with the other Panel members that, in terms of emphasis, I think to power the study and everything else, there should be that focus on the decompression.

DR. RAO: Thank you, Mr. O'Brien.

With respect to Question -- this was Question 5. Was there a subpart or was this the question? This is 5a. With respect to Question 5a, Mr. Melkerson, the Panel generally feels

that comparison of the device group in a new PAS to a historical device group would be inappropriate as a primary objective and that the primary objective should be comparison of the device group to a decompression, surgical decompression group. There is some concern that 24 months may be inadequate to entirely understand any differences between these two groups and that this period should be lengthened out. There is no clear consensus on the duration of time to which it should be lengthened out, but regardless, in addition to the clinical and radiographic parameters that have been listed, the cost of the different procedures, the cost of reintervention should also be factored into the results of any such post-approval study. I think -- is that adequate, Mr. Melkerson?

MR. MELKERSON: I'm going to defer to our OSB contact. She has a further clarification question.

DR. GHAMBARYAN: In general, I just have one more clarification for the comparison of a premarket cohort to the newly enrolled cohort. I have heard that some Panel members expressed there is a usability in that comparison to see how the clinicians perform in terms of implantation, for example. Currently, the proposal is for 24 months. I have heard that some of the Panel members suggested to make it 36 months, so I would like to hear more conclusive comments in regards to that comparison, as well.

DR. RAO: I'm not sure that anyone specifically talked about the duration for the device versus historical device group. I think the duration discussion was more on the device versus decompression group. And the consensus on the duration for the device versus decompression was that 2 years is too little and we need some longer duration. There's no clear consensus on what that duration should be, but that we should include, in

addition to all the other endpoints, also cost of the device, cost of the reintervention, all of the total costs for each group.

Let me just quickly go around. I don't want to delay this part of the question too long, but did anyone have any other thoughts on the duration of the device versus historical device group? On the duration of that study.

Mr. O'Brien.

MR. O'BRIEN: Joe O'Brien.

I would only point out, just from a logical perspective, that as I said, if you look at the "champions," the initial IDE study is now experiencing this 24- to 36-month "all of a sudden" spike in reoperations, then I would say that it's equally important then, if we're going to go out to a new group of clinicians to also understand that as well, to see if that's repeated or worse or whatever the case may be. So, even for that particular part of the study, to me it would seem important to extend it out.

DR. GHAMBARYAN: Thank you.

DR. RAO: Thank you very much.

Is that adequate, Mr. Melkerson?

MR. MELKERSON: Yes, thank you.

DR. RAO: Thank you.

DR. WYATT: Within the current outline for the long term follow-up of the IDE cohort, CT scans will not be done to evaluate spinous process fractures in the Superion and X-STOP groups. In addition, the proposed new cohort post-approval study states that CT scans will be done at 24 months only in symptomatic Superion subjects. Please discuss the

role of CT scans in evaluating subjects (in both treatment groups) for spinous process fractures in order to assess the long-term safety profile of the Superion device. Please specifically discuss the most appropriate time points for CT evaluation in order to identify all spinous process fractures, as well as whether there should be different algorithms in symptomatic and asymptomatic subjects. If different algorithms are recommended, please discuss the specific criteria that should be used to define "symptomatic" subjects.

DR. RAO: Thank you.

I think we have discussed this fairly substantially in the past, but I'll go around and start with Dr. Alander.

DR. ALANDER: Dr. Alander.

First off, I think I said before, I think that x-rays, plain x-rays are the primary way to identify this. Having said that, I do think that if you have a person with back pain at some point that you can't explain, but no leg pain, CT may be indicated to look at that. And then a second group would be a back pain with leg pain, and depending on what your x-ray would be, a CT might be helpful. I guess the question is in the first case, what do you about it? Do they have back pain? They have no leg pain. If you do a CT scan and say there's a spinous process fracture, are you going to operate on them, are you going to take the implant out? They have no leg pain, which is a primary goal of the surgery. If they have back pain and leg pain, then they may have settling and redevelopment of stenosis, and that would indicate that there may be an indication for decompression.

So, to address the question of an algorithm, I think there would be a different algorithm, whether they had back pain and no leg pain in the first group, or back pain and

leg pain in the second group. I would think that if you're going to make that decision, you're going to make it before 24 months. Musculature and soft tissue should be healed certainly before 3 months and rehabilitated. And if you're not making progress, I think at 3 months, that would be a reasonable time to start thinking about a CT scan.

DR. RAO: Thank you, Dr. Alander.

Dr. Haines.

DR. HAINES: Steve Haines.

I think a fundamental decision has to be made as to whether or not you want to study the role of CT in defining these fractures or not. If you do, then it needs to be done regularly, at least one early postop and annually or something like that through the study. Doing it just once, I mean, if finding it by CT isn't important enough to find it earlier than that, then you don't know what to do with the finding at 24 months. So that doesn't make any clinical -- really make any clinical sense. So that covers the time points. And you absolutely have to image everybody. If you do it selectively, again, you don't know what to do with the results. You may end up treating asymptomatic fractures when the pain is caused by something else because you don't know that everybody else in the asymptomatic group has one.

DR. RAO: Thank you, Dr. Haines.

Dr. Golish.

DR. GOLISH: I have nothing to add to the previous comments.

DR. RAO: Thank you, Dr. Golish.

Dr. Gilbert.

DR. GILBERT: I really don't either.

DR. RAO: Dr. Graf.

DR. GRAF: So the first portion of the question is to discuss the role of the CT in evaluating subjects. Of course, doing a CT on everybody will evaluate the subjects and likely be more sensitive and pick up more fractures. The clinical question is, what are we going to do with that? I do agree that if it's to be done, then it would be better to do it on everybody so that you can have something to do with this data. The second portion of the question, as far as the appropriate time points, in my opinion, this should be done immediately postop to determine, as I believe, with the mechanism of action, a lot of these fractures are likely intraop and from distraction and from the procedure itself, and they would be picked up immediately rather than over a period of time. They don't have to be a regular basis thereafter.

DR. RAO: Thank you, Dr. Graf.

Dr. Lyman.

DR. LYMAN: So, as I read this question, it looks like this -- about the long-term follow-up of the IDE cohort. They haven't had a fracture in the last 2 years, so why would we be exposing them to CT? So I wouldn't advocate CT at all in that IDE cohort. Now, thinking about the future in the postmarketing studies, then there may be a role for it, but that's not what the question is asking.

DR. RAO: Thank you, Dr. Lyman.

Dr. Yang.

DR. YANG: I think we've hashed this out quite a bit about risks and benefits of using

CT and the significance of spinous process fractures or lack thereof, so I don't have any other comments.

DR. RAO: Thank you, Dr. Yang.

Mr. O'Brien.

MR. O'BRIEN: Joe O'Brien.

I don't have anything to add on this.

DR. RAO: Thank you.

Dr. Trier.

DR. TRIER: The only comment that I would make is that using a CT scan for a nice-to-have data point is one thing, but because of the risk associated -- or not the risk, but the radiation for exposure for a CT scan, it just doesn't seem to justify doing them.

DR. RAO: Thank you, Dr. Trier.

Dr. Carrino.

DR. CARRINO: John Carrino.

I think the way it's stated, that having the CT done at 24 months in only symptomatic patients is kind of arbitrary and a bit problematic for the reasons that have been stated. You don't know what's happened in the non-symptomatic, and you don't have a baseline for comparison. So then we need to understand or to clarify what is the role and goal for the CT scan. If the role is to improve the detection and document the rate of spinous process fractures or other complications that CT can detect, then it needs to done uniformly across the entire cohort and at, I would think, at least two time points, which might be a baseline time point and then the 24 months. I'm not sure that that needs to be done, but if it was --

if those were the roles and goals that we're looking for CT, that would be one way to use it.

The other way to use the CT scan is to investigate people that have symptoms, and that the symptomatic configuration I would leave to the clinical colleagues, when they would use an investigation. As you can imagine, anybody who has a procedure or something and they come back and they have more or different or new or severe symptoms, they're going to be investigated with some imaging irrespective of what the protocol states, so to say we're only going to get CTs in somebody who's -- you've waited 2 years now for your symptoms to be worked up; that really doesn't fly in my experience.

So, to kind of state that I'm kind of neutral on whether CT needs to be used or not -- but if the role and goal is to get a good documentation and characterization of the fractures, then it should be applied uniformly so all the cohort -- and that at least two points. But I don't feel strongly that it has to be done. We can use radiography, and then CT would either not be part of the study or only be included when you need to investigate new symptoms or unremitting symptoms.

DR. RAO: Thank you, Dr. Carrino.

Mr. Melkerson, with regard to Question 5b, the Panel generally believes that there may be a limited role for CT scans in patients who have significant symptoms, either back and/or leg pain. The Panel generally believes that CT scans have little to no utility in routine monitoring of study patients. There may be a limited role for CT scans in study patients if a separate question as to the utility of the CT scan itself, in determining either prognosis or treatment options for fractures, was part of the study objective.

Is that adequate, Mr. Melkerson?

MR. MELKERSON: Yes, thank you.

DR. RAO: Is that adequate, Dr. Wyatt?

DR. WYATT: Yes, thank you.

DR. RAO: Thank you. Do you have any further questions?

DR. WYATT: Not at this time.

DR. RAO: At this time the Panel will hear summations, comments, or clarifications from the FDA.

DR. WYATT: The FDA has no further comments, questions, or clarifications at this time.

DR. RAO: Thank you.

At this time the Panel will hear summations, comments, or clarifications from the Sponsor. You have 15 minutes.

DR. NUNLEY: Pierce Nunley. We've been working long and hard today. I'll keep it much shorter than 15 minutes.

I think the first thing, to kind of bring us back, as we've had these great deliberations and really appreciate all the comments from everyone here today, is bring it back to what does 21 C.F.R. 860.7 have us look to, and that is, is the device safe and a reasonable assurance of safety for the probable benefits that outweigh any probable risks and the absence of any unreasonable risks of the device. We think that the safety of Superion compared to X-STOP in this study, we've shown, has similar types of adverse events, it has similar rates of adverse events, the device- and procedure-related adverse events are comparable, and that the reoperations and revisions were similar for both Superion and

X-STOP.

Going back to the fracture observations, we've demonstrated that these have been evaluated by MMI, and we think we generally agree that they tend to be clinically not a significant issue; there's not been an increase in additional treatments, and we do know that many of them do heal at 24 months. The primary spinous process fractures, we do know that -- we've discovered that shallow placement and height of the spinous process are factors that increase the rate of that, and we intend to use that to mitigate the risks in the postmarket time period in the postmarket studies and believe we'll be successful at that.

As far as the safety of it compared to other treatments, when we look at it against the IDE coflex study Level I data, we find that it's quite comparable and more favorable in perioperative metrics. We also note that it has fewer complications in this large Medicare cohort than alternative treatments.

And then to go back to the direct decompression, I think we get stuck a little bit on thinking that the gold standard means that everybody's going to do well. And if we look carefully at the literature, both the SPORT trial, which noted up to, I believe it's 12% revision rate and then Berven's paper in *Spine*, which looked at a 5,000 patient Medicare database, I think it was 2013, noted readmission rate of 8 to 10% per year. And at 3 years, the readmission rate was 24% for decompression, readmission, and surgery, either a surgery with a decompression or fusion. So when you look at those two groups, decompression alone is not benign. There are revision surgeries, just like this. So we would go back to say this is a primary treatment.

Effectiveness. Again, as looking to 21 C.F.R. 860.7, we need to show that the

significant portion of the target audience, when accompanied by adequate directions for use and warning, the device is proved to be reasonable, have the assurance of efficacy. And we believe we've shown that clearly in the modified intent-to-treat and X-STOP, although those numbers, in and of themselves, as we've discussed multiply here today, may appear to be low. As been said several times, we've achieved over 80% success in all four components of the primary endpoint and also had very robust data and that we received in the posterior probability of non-inferiority equal to .9927, which is well above the .958 for the Bayesian analysis. And we've seen improvement from the baseline and the outcome measures, and we've seen the durability to 36 months, so it's not just beyond 24. Radiographic data, we do believe, shows evidence of extension blocking and do understand the shortcomings that have been discussed today, but still believe that shows that. So the balance of the data that we believe has a significant portion of the population did achieve consistent, meaningful, and lasting clinical improvement.

Going into this a little bit more, you've seen these diagrams before about three or four times in our presentation, but again, we've met clinical success, reoperation success, no additional treatment success, and no complication success in greater than 80% of patients. And we maintained this out to 36 months. Just briefly, when we talk about composite scores, we want to remind that as you add each composite, you take down the score. You never can go higher. As you add a second and a third and a fourth, your endpoint is going to go further down. And we note that the Mobi-C trial, which I was a principal investigator in, one of the principal problems we had was people said ACDF is a great surgery, and when the FDA defined an alternative success definition of 60%, that may

seem low, but the final study showed, in the ACDF group, 37.4% success in the composite score for ACDF. We know that ACDF two-level surgery is not 37.4%, so we have to look at these composite scores for what they are and, as people have stated, to compare them between different studies. And we feel that we've done that quite nicely in multiple points and multiple subscales. So a significant portion of the population did achieve consistent, meaningful, and lasting clinical improvement.

And, finally, the FDA wants to have you vote on the probable benefits, do they outweigh the probable risks in the proposed indications. The benefits of Superion, we believe, are clinically significant; we believe we've demonstrated long-term relief to 36 months. We've noted a continued reduction in range of motion, it's a less invasive procedure, it preserves the surrounding anatomy, and there is no demonstrated risk of migration or dislodgements, which we all agree can be a problematic situation. So Superion is a valid option for treatment of moderate stenosis.

And in the risk profile, the adverse event profile, the radiographic and reoperation and revision rates, again, we believe that these risks can be mitigated by further surgeon training and labeling and postmarket studies. And the relative efficacy, the perioperative metrics, the postoperative complications, and the reoperative revisions, again, the Level I data supports that interspinous process spacers and the risk-benefit profile is appropriate. We've looked at this at leg pain and comparing it to epidural steroids and to decompression and again to show with the ZCQ, comparing those two, we find very similar populations.

So, in summary, we do believe that the benefits of Superion have been shown in this Level I study. We also believe that the risk of reoperation, although 80% of the patients did

not require reoperation, that it's adequate, that the spinous process fracture rate, although is a significant finding and we need to study more about that and we look forward to working with the FDA to do that, the majority were asymptomatic. And, finally, that the risk mitigation we do believe is present.

So, in closing remarks, we feel strongly we've demonstrated the safeness of this device compared to X-STOP. We believe that the clinical significant improvement in pain and function is seen in the majority of the population, greater than 80%. And we also believe that the benefits are comparable to the X-STOP control and alternative treatments without risks associated with direct decompression or fusion.

We greatly appreciate your time and your service and thank you.

DR. RAO: Thank you, Dr. Nunley.

Before we proceed to the Panel vote, I would like to ask our non-voting members -- Dr. Trier, our Industry Representative; and Mr. O'Brien, our Patient Representative -- if they have any additional comments.

Dr. Trier.

DR. TRIER: Dr. Trier speaking.

This Panel was convened not only to discuss the non-voting questions that FDA has posed but, you know, primarily it is convened to be able to address the issues of efficacy, safety, and then the risk-benefit profile. And based on the data that has been presented, based on the IDE study that was conducted, it seems to me that the data that can be considered to answer these questions has been presented and would lead you to make a certain determination about this device. I know that the vote is yours, the data is here. Ask

for Panel consideration based on the data. Thank you.

DR. RAO: Thank you, Dr. Trier.

Mr. O'Brien, do you have any comments?

MR. O'BRIEN: Joe O'Brien.

I would again applaud VertiFlex for the work that they've done. I think the product appears to me as a very innovative -- I like the design and the approach, et cetera. I do think that in terms of the data that I saw relative to the objective of non-inferiority to X-STOP was accomplished. Relative to a lot of the discussion and concerns that I expressed from a patient perspective, I think the jury is still out, in my mind, as I read through this in terms of its efficacy. And as a patient alternative, I think -- and its safety even, actually, on a long-term basis, and to me it seems like there's still more work to be done, and I applaud the postmarket studies that have been proposed because I think those are important questions to answer, whether it's postmarket or not, depending on what the voting is. So that's, I guess, where I'm at.

DR. RAO: Thank you, Mr. O'Brien.

We are now ready to vote on the Panel's recommendation to the FDA for the Superion spinous process spacer device, Superion VertiFlex, Incorporated. The Panel is expected to respond to three questions relating to safety, effectiveness, and benefit versus risk. Lieutenant Commander Anderson will now read three definitions to assist in the voting process. Lieutenant Commander Anderson will also read the proposed indication for use statement for this device.

LCDR ANDERSON: The Medical Device Amendments to the Federal Food, Drug and

Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket approval applications that are filed with the Agency. The PMA, the premarket approval application, must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety as defined in 21 C.F.R. Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

Effectiveness as defined in 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence as defined in 21 C.F.R. Section 860.7(c)(2) is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of

safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking significant details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations, as defined in paragraph (f) of this section, unless the Commissioner authorizes reliance upon other valid scientific evidence which the Commissioner has determined is sufficient evidence from which to determine the effectiveness of a device, even in the absence of well-controlled investigations.

The Sponsor has proposed the following indications for use: The Superion Interspinous Spacer is intended to treat skeletally mature patients suffering from pain, numbness, and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of lumbar spinal stenosis, with or without Grade 1 spondylolisthesis, confirmed by x-ray, MRI, and/or CT evidence of thickened ligamentum flavum, narrowed lateral recess, and/or central canal or foraminal narrowing. The Superion ISS is indicated for those patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness and/or cramping, with or without back pain. The Superion ISS may be implanted at one or two adjacent lumbar levels in patients in whom treatment is indicated at no more than two levels, from L1 to L5.

Panel members, please use the buttons on your microphone to place your vote of yes, no, or abstain to the following three questions. I will now read the voting questions.

Voting Question 1 reads as follows: Is there a reasonable assurance that the VertiFlex Superion ISS is safe for the indication for use as treatment for pain, numbness,

and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of moderate lumbar spinal stenosis, with or without Grade 1 spondylolisthesis?

Please vote yes, no, or abstain.

(Panel vote.)

LCDR ANDERSON: I'm still waiting for two votes.

(Pause.)

LCDR ANDERSON: Okay, great. Okay.

Voting Question 2: Is there a reasonable assurance that the VertiFlex Superion ISS is effective for use in patients who meet the criteria specified in the proposed indications?

Please vote now yes, no, or abstain.

(Panel vote.)

LCDR ANDERSON: Okay.

All right, the third and final voting question reads as follows: Do the probable benefits of the VertiFlex Superion ISS outweigh the probable risks for use in patients who meet the criteria specified in the proposed indications?

Please vote yes, no, or abstain.

(Panel vote.)

LCDR ANDERSON: Okay, the votes have been captured, and I will now read the votes into the record.

On Question 1, the Panel voted 5 yes, 2 abstain, 1 no that the data shows reasonable assurance that the Superion Interspinous Spacer is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 5 yes, 2 abstain, 1 no that there is reasonable assurance that the Superion Interspinous Spacer is effective for use in patients who meet the criteria specified in the proposed indication.

On Question 3, the Panel voted 4 yes, 2 abstain, 2 no that the benefits of the Superion Interspinous Spacer outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

The three voting questions are now complete.

DR. RAO: Thank you, Lieutenant Commander. What's the country coming to when an Indian guy has to tell a Lieutenant Commander how to pronounce "principally"?

(Laughter.)

DR. RAO: I will now ask the Panel members to discuss their votes. I would like to go around the table and have each Panel member state how they voted on each question so it can be entered into the public record. Please also discuss the reasoning for your vote. If you answered no to any question, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer.

Why don't we start with Dr. Yang?

DR. YANG: So I voted yes to Question 1, 2, and 3. Just brief -- I mean, in comparison to everything in my personal experience as a clinician, the safety of this device is not a concern to me. Reasonable assurance, yes, I think there's reasonable assurance. And yes, I think the benefits outweigh the potential risks at this point.

DR. RAO: Thank you, Dr. Yang.

Dr. Lyman.

DR. LYMAN: I actually abstained on all three questions, and the reasons are multi-factorial. One is I did never have a clear perception from anyone whether or not this technology represented a step forward in the mechanical properties and the way that it was designed. Second, I didn't get any sense from the clinicians whether or not they felt that this was an appropriate indication, an appropriate use of this technology in these patients. And there seems to be quite a few adverse events associated with this, including high revision rate. And even though it wasn't statistically significant at 2 years, it was trending in that direction, and I suspect that they were underpowered for that particular endpoint.

But I also didn't feel like I had enough information to vote no on any of these based on that information, and I stated before, the composite endpoint and the patient-reported outcomes representing effectiveness were a mixed bag for me based on the way that they were presented.

DR. RAO: Thank you very much, Dr. Lyman.

Dr. Graf.

DR. GRAF: I voted yes on all three. I believe that the product itself is safe. For the second item, was difficult for me to answer. I did vote that the reasonable assurance would be that it would be effective. The third question, because I thought it was safe, I didn't have a problem with answering if the benefits outweighed the risks.

DR. RAO: Thank you very much, Dr. Graf.

Dr. Gilbert.

DR. GILBERT: So, to Question 2, I voted yes. That was the effective question. I think that the weakness of the study design comparing to another device that had relatively low

success was a weakness of the approach, but it was worked out with FDA, and I think you did meet that bar, so I voted yes. I voted no to Question 3 -- I'm not doing them in order. I voted no in Question 3 because as I thought through it, I'm not convinced we understand all of the probable risks, and so I couldn't say yes, that the benefits outweighed those risks because I'm not assured, for myself, that we've identified and properly assessed all of those risks. And so as a result of that, in Question 1, the safety, I couldn't then make a vote of yes to the safety without better understanding the probable risks, so I voted no.

DR. RAO: Thank you very much, Dr. Gilbert.

Dr. Golish.

DR. GOLISH: Are we discussing all three responses now? Yeah.

I voted yes on safety. I think the Sponsor did a good job of mitigating the perceived risk of the spinous process fractures as a safety issue. With respect to Question 2, I voted no. The Sponsor did a remarkable job with a well-designed study, a breathtaking rate of follow-up, and relatively tight-looking data at the end, but as I earlier had the opportunity to say, I think the design is intrinsically challenged, which led me to vote no on No. 3. But I do believe if the device is approved, that the proposed randomized trial follow-up study with respect to decompression would do much to ameliorate those concerns.

DR. RAO: Thank you, Dr. Golish.

Dr. Haines.

DR. HAINES: Steve Haines.

My problem is with the way the questions are proposed and the way that interacts with the study design. I am not convinced that the control group was treated in a way for

which there is valid scientific evidence to support the efficacy and safety of the device, and therefore, I would have a great deal of difficulty answering these questions in the affirmative. On the other hand, I think the Sponsor has met the proposed criterion of demonstrating non-inferiority, so I would have a great deal of difficulty answering no to any of these questions, and therefore, I abstained on all three.

DR. RAO: Thank you very much, Dr. Haines.

Dr. Alander.

DR. ALANDER: Dr. Alander.

I voted yes to all three. I think they met the criterion as established.

DR. RAO: Thank you, Dr. Alander.

Dr. Carrino.

DR. CARRINO: Yes, I voted yes on all three questions. I think the most robust answer was No. 1 for demonstrating safety of this device. I think with Question 2, the reasonable assurance that it's effective, they did demonstrate what they set out to do as a non-inferiority, and I think the point was brought up that maybe that shouldn't have been the device that they compared it to, but it seems like that was a research plan that was negotiated or thought out with the Agency, and they went forward with that, so that's what they accomplished. And then in terms of probable benefits versus risks and doing a lot of not taking care of but imaging patients, postoperative patients, and seeing a number of those, I thought that the benefits of doing something like this, doing a minimally invasive approach, could have a role and they did have enough evidence for that. So that's the reason for doing all three yes, but --

DR. RAO: Thank you very much, Dr. Carrino.

At this point, I would like to thank the distinguished members of the Panel for all their hard work and attentiveness and diligence in reviewing the documents and being prepared for today's discussion. I would like to thank Lieutenant Commander Anderson, Mark Melkerson, and the outstanding FDA personnel. I'd also like to thank the Sponsor for a lot of hard work, for staying on time, and for their contributions to today's Panel meeting.

Mr. Melkerson, do you have any final comments?

MR. MELKERSON: I would just like to echo my thanks to the Panel for your time, efforts, and putting up with our cold weather. As far as the Sponsor and the review team, I think continued interaction is going to be necessary to move forward. But thank you for everybody's time, efforts, and input.

DR. RAO: Thank you, Mr. Melkerson.

I now pronounce the February 20th, 2015 meeting of the Orthopaedic and Rehabilitation Devices Panel closed.

(Whereupon, at 4:37 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

ORTHOPAEDIC AND REHABILITATION DEVICES PANEL

February 20, 2015

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TIMOTHY J. ATKINSON, JR.

Official Reporter